References. 1. Liu X, et al. Recent Advances in the Clinical Value and Potential of Dexmedetomidine. J Inflamm Res. 2021;14:7507-7527. **2.** Elgebaly AS, et al. Sedation effects by dexmedetomidine versus propofol in decreasing duration of mechanical ventilation after open heart surgery. Ann Card Anaesth. 2018;21(3):235-242. **3.** Precedex injection product information. Latest HA approved date: Apr 3, 2023. **4.** Kang D, et al. The correlation of heart rate between natural sleep and dexmedetomidine sedation. Korean J Anesthesiol. 2019;72(2):164-168. **5.** Precedex Premix injection product information. Latest HA approved date: Apr 3, 2023.

ACC Acute and Critical Care

pISSN 2586-6052
eISSN 2586-6060

Acute and Critical Care

Vol.38 No.4 November 2023

Volume 38 • Number 4 • November 2023

Pages 389-516

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† In SECURE trial, significantly fewer patients reported events considered drug-related by the investigator for isavuconazole than for voriconazole (109 [42%] vs 155 [60%]; P<0.001). Additionally, fewer isavuconazole-treated patients experienced drug-related treatment-emergent adverse events within the following system organ classes: hepatobiliary disorders, laboratory investigations, eye disorders, and psychiatric disorders. Permanent drug discontinuation due to treatment-emergent adverse events were less common with isavuconazole (37 [14%] vs 59 [23%]). Permanent drug discontinuation due to drug-related adverse events was lower for isavuconazole than for voriconazole (21 [8%] vs 35 [14%]).[5]

[Study design] SECURE: This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice–web response system, stratifi ed by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). The investigators tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. 527 adult patients were randomly assigned (258 received study medication per group) between March 7, 2007, and March 28, 2013.[5]

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References 1. Jenks JD, et al. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther. 2018;12:1033–1044. **2.** CRESEMBA IV Prescribing information (Final revision date: 2021.12.08) **3.** CRESEMBA Capsule Prescribing information (Final revision date: 2021.12.08) **4.** Tissot F, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433-444. **5.** Maertens JA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760-769.

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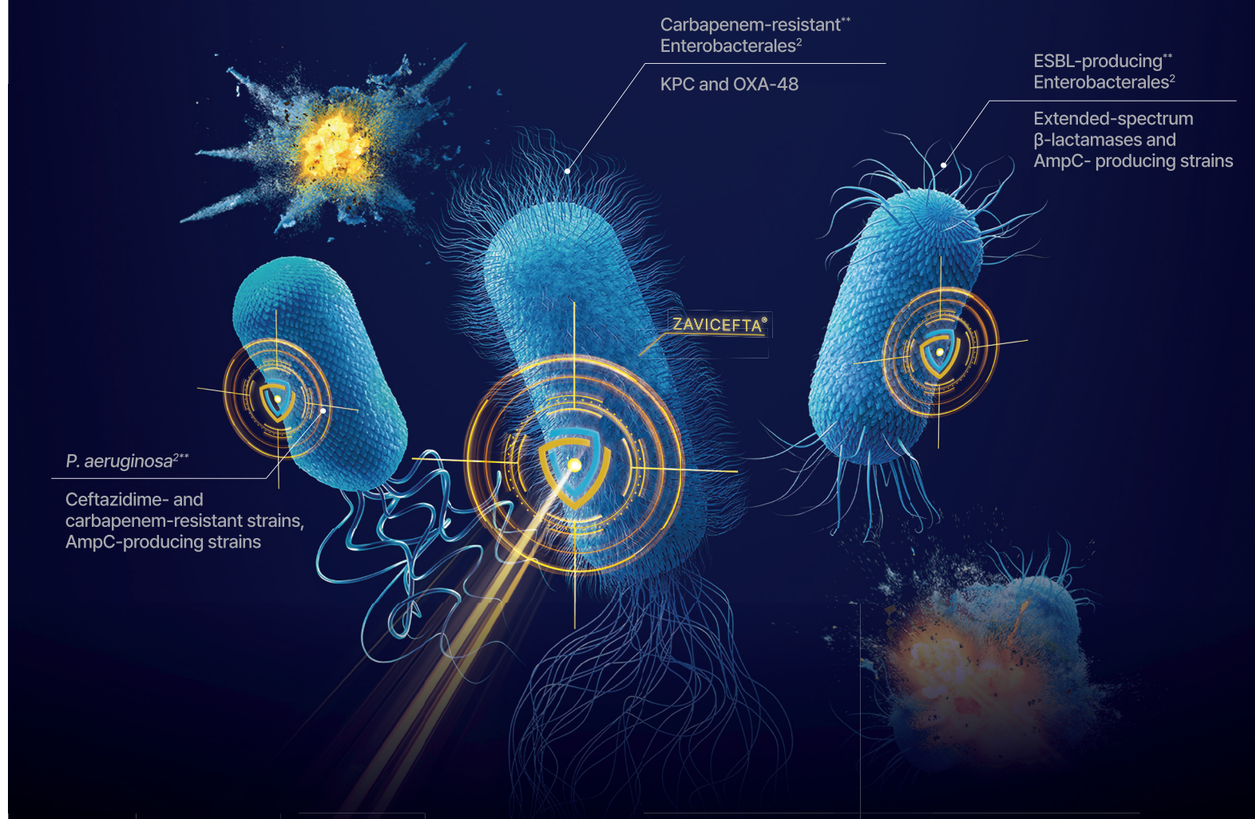

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References 1. Giurazza R, et al. Emerging Treatment Options for Multi-Drug-Resistant Bacterial Infections. Life (Basel). 2021 Jun 3;11(6):519. **2.** 자비쎄프타주 제품설명서 (개정년월일: 2023.01.31) **3.** Shirley M. Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections. Drugs. 2018 Apr;78(6):675-692. **4.** Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. J Antimicrob Chemother. 2016 Oct;71(10):2713-22.

[주요 안전성 정보*] 이 약의 투여를 시작하기 전, 환자에게 세프타지딤, 다른 세팔로스포린 또는 다른 베타락탐계 항생제에 과민반응의 병력이 있었는지 확인해야 한다. 페니실린, 모노박탐 또는 카바페넴에 중증이 아니었던 과민반응 병력이 있는 환자에서도 이 약 투여 시 주의가 요구된다. • 이 약 투여 후 Clostridioides difficile에 의한 설사(CDAD)가 보고되었으며, CDAD의 증상은 경증에서 생명을 위협하는 정도까지 다양하다. • 세프타지딤과 아비박탐은 신장으로 배설되므로, 신기능장애 정도에 따라 용법·용량을 참조하여 투여용량을 감량한다. 경증 신장애 환자(추정 CrCL: 50초과 - 80 mL/min이하)에서 용량 조절은 필요하지 않다. • 간장애 환자에서 용량 조절은 필요하지 않다.

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ACC Acute and Critical Care

Volume 38 No. 4 November 2023
Published on November 30, 2023

| pISSN 2586-6052 | eISSN 2586-6060
https://www.accjournal.org

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Scope: Its scope includes basic, experimental, and translational research as well as clinical studies relating to all fields of critical illness.
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This work was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

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This journal is primarily intended for scientific researchers and personnel who work for acute, critical care. However, its readership can be expanded to other positions: students can understand recent trends in acute, critical and intensive care medicine; physicians can obtain recent topics and cases for continuing education; policy makers are able to reflect the results of the articles to nation-wide public health and science promotion policies.

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Publisher: **Gee Young Suh, M.D., Ph.D., FCCM** (*Sungkyunkwan University, Korea*)
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Printed by **M2PI**
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
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Acute and Critical Care

| pISSN 2586-6052 | eISSN 2586-6060
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Acute and Critical Care

| pISSN 2586-6052 | eISSN 2586-6060
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Acute and Critical Care 2023 November 38(4):389-398
https://doi.org/10.4266/acc.2023.01368

| pISSN 2586-6052 | eISSN 2586-6060

Plasma biomarkers for brain injury in extracorporeal membrane oxygenation

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Extracorporeal membrane oxygenation (ECMO) is a life-saving intervention for patients with refractory cardiorespiratory failure. Despite its benefits, ECMO carries a significant risk of neurological complications, including acute brain injury (ABI). Although standardized neuromonitoring and neurological care have been shown to improve early detection of ABI, the inability to perform neuroimaging in a timely manner is a major limitation in the accurate diagnosis of neurological complications. Therefore, blood-based biomarkers capable of detecting ongoing brain injury at the bedside are of great clinical significance. This review aims to provide a concise review of the current literature on plasma biomarkers for ABI in patients on ECMO support.

Key Words: acute brain injury; biomarkers; extracorporeal membrane oxygenation

Review Article

Received: October 27, 2023
Revised: November 24, 2023
Accepted: November 24, 2023

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INTRODUCTION

Over the past 30 years, extracorporeal membrane oxygenation (ECMO) has been increasingly deployed to provide life-saving circulatory support to patients with refractory pulmonary and cardiac pathology [1]. Venoarterial (VA)-ECMO is used as the rescue of refractory cardiac failure and venovenous (VV)-ECMO is used for refractory respiratory failure. Despite its benefits, current literature indicates an overall ECMO survival rate of 29%, with acute brain injury (ABI), including acute ischemic stroke (AIS), intracranial hemorrhage (ICH), and hypoxic-ischemic brain injury, being a leading cause of morbidity and mortality [2]. Further, ABI confers a two- to three-fold increase in mortality risk for patients on ECMO [2-4]. Standardized neuromonitoring protocols improve the detection of ABI and include iterative neurological exams, near-infrared spectroscopy, transcranial doppler, electroencephalograms, and somatosensory evoked potential and neuroimaging studies (Figure 1) [3,4].

However, neuroimaging during ECMO is challenging. Head computed tomography (CT) scans lack sensitivity to detect early and small ischemic events. Moreover, head CT scans are obtained in only 30% of ECMO patients due to the increased risks of transporting patients while cannulated for ECMO [3]. Brain magnetic resonance imaging (MRI) is more sensitive

for identifying ischemia but MRI with high-strength magnetic fields (1.5–3T) is incompatible with ECMO [5]. Additionally, most patients receiving ECMO support would not be stable enough to undergo a prolonged imaging study outside of the intensive care unit. To overcome these limitations, the development and validation of accessible plasma biomarkers that are sensitive and specific for ABI are necessary. Consequently, there has been a recent interest in plasma biomarkers for patients on ECMO (Figure 2). The purpose of this review is to concisely consolidate and critically appraise our current understanding of plasma biomarkers and their role in monitoring and prognostication of ABI and their applicability in patients on ECMO support.

KEY MESSAGES

- A comprehensive evaluation and critical appraisal of a range of biomarkers including neuron-specific enolase, glial fibrillary acidic protein (GFAP), inflammatory cytokines, microRNA, tau protein, neurofilament light chain (NfL), mitochondrial DNA, cell-free DNA, lipidomics, and metabolomics have been outlined, revealing their potential in predicting acute brain injury and neurological outcomes in extracorporeal membrane oxygenation (ECMO) patients.
- GFAP and NfL are biomarkers that offer the most promise for clinical utility.
- There is a need for further multicenter research to develop standard thresholds to optimize the application of these biomarkers in patients on ECMO support.

BIOMARKERS STUDIED IN ECMO

Biomarkers in VA-ECMO

Neuron-specific enolase

Neuron-specific enolase (NSE) is a glycolytic enzyme prevalent in neurons and neuroendocrine cells [5]. NSE bloodstream levels, which begin to increase several hours after neuronal damage and peak at 48 hours post-injury, are a potential biomarker for brain injury in patients undergoing ECMO [6,7]. Several studies have focused on elucidating the role of NSE in various clinical settings. A prospective multicenter study involving 623 out-of-hospital cardiac arrest (OHCA) survivors revealed a significant difference in median NSE levels between patients with non-shockable and shockable rhythms (104.6 ng/ml [range, 40.6–228.4] vs. 25.9 ng/ml [range, 16.7–53.4], P<0.001) [6]. In a retrospective multicenter study on 70 traumatic brain injury (TBI) patients, higher NSE concentrations corresponded with increased injury severity and adverse neurological outcomes [8].

The utility of NSE as a biomarker for patients on ECMO is still under investigation. A prospective study involving 80 pediatric ECMO patients indicated elevated NSE levels in those developing neurological complications [9]. Specifically, elevated plasma concentrations of NSE, with a cutoff of 62.0 ng/ml, were associated with increased odds (adjusted odds ratio, 2.89) of unfavorable outcomes, measured by Pediatric Cerebral Performance Category, at hospital discharge [9]. These findings are consistent with another retrospective single-center study of 30 adults in a VA-ECMO cohort, which showed that NSE peak values above a cutoff of >100 μg/L had a sensitivity and specificity for mortality of 0.53 and 0.82, respectively [10].

However, it's important to highlight that the specificity of NSE in ECMO patients may be compromised by erythrocyte hemolysis, a frequent occurrence in ECMO, which can lead to elevated NSE levels, complicating its reliability in detecting ABI and predicting neurological outcomes [11]. Future prospective

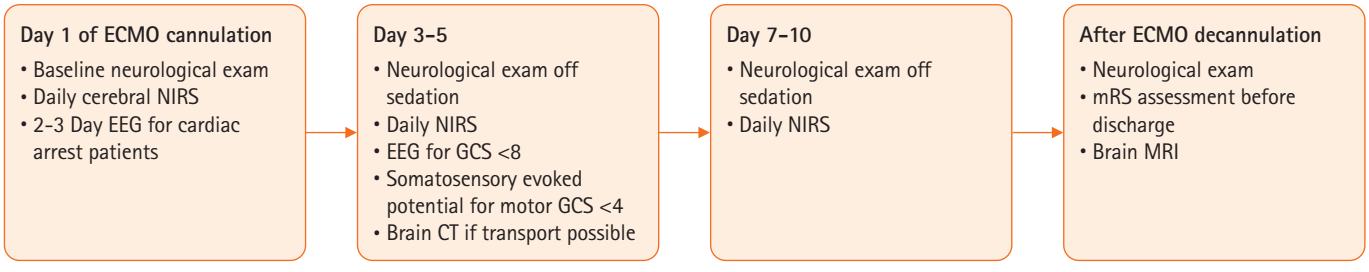

Figure 1. Standardized neuromonitoring protocol. ECMO: extracorporeal membrane oxygenation; NIRS: near-infrared spectroscopy; EEG: electroencephalogram; GCS: Glasgow Coma Scale; CT: computed tomography; mRS: modified Rankin Scale; MRI: magnetic resonance imaging. Adapted and Retrieved from Ong CS, et al. J Thorac Cardiovasc Surg 2023;165:2104–10 [4], to which biomarkers could be supplementary once more studied in ECMO.

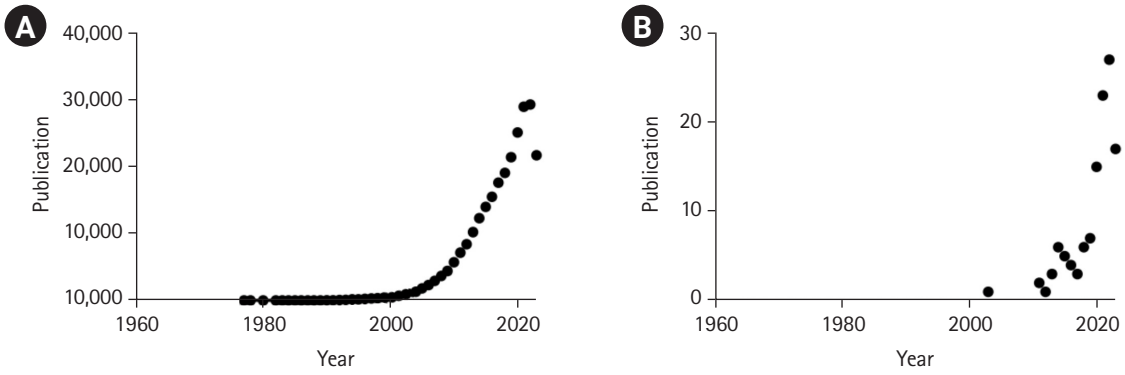

Figure 2. (A) The number of publications over time looking at "biomarker," "surrogate marker," or "surrogate endpoint." (B) The number of publications over time looking at "biomarker", "surrogate marker" or "surrogate endpoint" and extracorporeal membrane oxygenation.

multicenter research is necessary to understand specific NSE thresholds and dynamic kinetics in relation to ABI in ECMO patients.

Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is a specific type of intermediate filament protein, involved in the structural integrity and functioning of astrocytes within the central nervous system (CNS). The unique localization of GFAP to astrocytes in the brain emphasizes its potential as a sensitive biomarker for detecting brain injuries. Astrocytes undergo astrogliosis—a reactive process involving cellular proliferation and increased GFAP production—indicating neuronal damage [12]. GFAP is elevated within about 2 hours following injuries such as AIS [13-15], cardiac arrest [16,17], and TBI [18-22], peaking at 48–72 hours [23], and thus may be useful for monitoring both neurologic and non-neurologic complications in ECMO.

In a pediatric single center VA-ECMO cohort (n=80), GFAP levels were measured by immunoassay at 6 and 12 hours, and then every 24 hours after cannulation [9]. GFAP levels were found to be significantly elevated in children on ECMO who experienced ABI compared with children who did not, with a median of 5.9 versus 0.09 ng/ml (P=0.04) [9]. Additionally, higher GFAP levels were found in non-survivors compared to survivors. GFAP levels over 0.436 ng/ml were associated with increased odds ratio (OR) of brain injury (OR, 11.5; 95% confidence interval [CI], 1.3–98.3) and mortality (OR, 13.6; 95% CI, 1.7–108.5) [9]. However, this study was limited by the small sample size and the difficulty of accurately diagnosing ABI. A pilot single-center study by Kapoor et al. [24] (n=20) corroborated these findings in adults on VA-ECMO support, with median plasma GFAP levels noted to be significantly higher for patients who developed ABI vs. without (5.17 ng/ml vs. 0.16 ng/ml, P=0.047). The findings from these pilot studies warrant further research in larger cohorts to validate and define their clinical applications.

Tau

Tau proteins are microtubule-associated proteins involved in stabilizing the cytoskeleton, particularly in unmyelinated axons of the CNS [25]. While they are most abundant in neurons, they are also found in astrocytes and oligodendrocytes [25]. Like neurofilament light chain (NfL), tau protein released into the cerebrospinal fluid (CSF) can potentially be used as a biomarker indicating axonal damage. Tau has been most heavily studied in its misfolded aggregate form in Alzheimer disease and other forms of dementia, such as chronic traumatic encephalopathy in athletes playing contact sports [26,27].

Elevated tau has shown promise as a marker for adverse clinical outcomes following TBI. In a pilot, single-center prospective study of 16 patients, microdialysis catheter measurement of tau from the brain extracellular space following TBI correlated with a lower Glasgow Coma Scale (GCS) score 6 months after injury (r=–0.6, P=0.018) [28]. Additionally, tau levels were highest when catheters were near the area of the contusion, verifying the use of tau as a marker of axonal damage [26]. These conclusions were strengthened by another single-center prospective study (n=50), which showed that CSF tau levels correlated with AIS severity (P<0.05). In this study, higher CSF tau levels were also correlated with a worse outcome defined by the modified Rankin Scale (mRS) score at 12 months [29]. In an international multicenter prospective study (n=689), increased serum tau soon after OHCA was predictive of poor neurological function at 6 months, as measured by

the Cerebral Performance Categories (CPC) scale. At 48 hours following cardiac arrest, the median tau levels were 49.5 ng/L in the poor outcome group, and only 1.2 ng/L in the favorable outcome group (P<0.0001) [30]. Tau levels may be useful for more extended neuromonitoring, as while elevations begin as early as 6 hours post-injury, peak elevations are as late as 6 days following injury [31].

Despite the promising results of tau protein predicting outcomes in neurological diseases, evidence is very limited in ECMO patients. A pilot single-center prospective observational cohort study by Kapoor et al. [24] (n=20) reported a higher trend in plasma tau values for patients with ABI vs without ABI on VA-ECMO (1.87 ng/ml vs. 0.44 ng/ml, P=0.62). This study was limited by its sample size and was unable to reach appropriate power for statistical significance. While tau shows promise as a biomarker after TBI and cardiac arrest, its utility for patients on ECMO needs to be further explored.

Neurofilament light chain

Neurofilaments are intermediate filaments that help comprise the cytoskeleton of neurons. The triplet consists of three subunits, including NfL, neurofilament medium chain, and neurofilament heavy chain [32]. NfL is a neuron-specific protein residing in the cytoplasm of large, myelinated axons [32]. NfL has been studied as a potential biomarker, as its release into the CSF as early as several hours after injury can indicate neuronal death and more specifically axonal damage [33,34]. To date, NfL has been most thoroughly studied in multiple sclerosis, TBI, and cardiac arrest, and its application in other neurologic disorders has recently been explored including stroke, lysosomal storage disorders, amyotrophic lateral sclerosis, and frontotemporal dementia.

NfL has shown promise as a marker for outcome prediction in patients with OHCA. An international, multi-center (29 sites) prospective study of 782 adults demonstrated that serum NfL levels measured 1–3 days after OHCA were sensitive and specific for worse neurological outcomes by CPC score at 6 months, and this prognostic performance exceeded that of other biomarkers and standardized neuromonitoring (CT, somatosensory evoked potentials, electroencephalogram, and neurological exam) [35]. A multicenter prospective study of 248 adults validated these findings and found that median serum NfL concentrations 48 hours after OHCA was 0.019 ng/ml in patients with good neurological outcomes by CPC score and 2.343 ng/ml in those with poor neurological outcomes (P<0.001) [36]. In a retrospective multicenter observational study (n=428) looking at CPC outcomes for both OHCA and in-hospital cardiac arrest (IHCA), NfL at 12 hours was superior to NSE at 24 hours (area under the curve [AUC]: 0.93 vs. 0.83 for OHCA and AUC: 0.87 vs 0.71 for IHCA) [37]. NfL at 48 hours was superior to NSE at 48 hours (AUC: 0.97 vs. 0.90 for OHCA, and AUC: 0.90 vs. 0.77 for IHCA) [37].

A pilot prospective single-center cohort study (n=20) reported a significant difference in NfL values for patients with ABI vs without ABI on VA-ECMO (13.6 ng/ml vs. 3.42 ng/ml, P=0.007), which may be better than GFAP and tau protein in predicting ABI and neurological outcomes in ECMO patients [24]. In summary, serum NfL appears to be the most promising biomarker with consistent demonstration of high sensitivity and specificity across various forms of brain injury. Further studies to determine accurate cutoffs are warranted for ECMO patients.

Biomarker Applications Studied in VV-ECMO

MicroRNA

MicroRNAs (miRNAs) are a class of single-stranded, non-coding RNA fragments involved in regulating gene expression in many pathways [38]. While currently difficult to implement miRNA in a critical care setting due to the cost and time needed to determine miRNA sequencing signatures, a prospective study in 11 adult VV-ECMO patients with severe acute respiratory distress syndrome (ARDS) found that serum levels of 13 miRNAs in were markedly upregulated (vs. those with less severe disease) as measured by Sequential Organ Failure Assessment (SOFA), respiratory ECMO survival prediction score, and Simplified Acute Physiology Score (SAPS) II [38]. miRNAs increased in severe ARDS were found to be members of tissue remodeling, blood coagulation, and immune regulation pathways, in line with processes found to contribute to further injury in ARDS patients [38]. While not specifically studying neurological outcomes, as miRNA sequencing becomes more available and cost-effective, similar miRNA upregulation signatures could be identified specifically for neurological injury. The breadth of available miRNAs means that biomarkers could be unique according to tissue type, and even to processes such as ischemic and hemorrhagic stroke.

Biomarker Applications Studied in VA-ECMO and VV-ECMO

Inflammatory cytokines

Inflammatory cytokines such as interleukin (IL)-6, IL-1, IL-8, and tumor necrosis factor (TNF)-α are small, secreted mole-

cules controlling cell-cell interaction in the setting of inflammation regulation [39]. While it has been well-established that inflammatory cytokines rise throughout the duration of ECMO therapy [40], few studies have focused on inflammatory cytokines as predictors of neurological injury in the setting of ECMO. One prospective pediatric study of 99 patients undergoing both VA-ECMO and VV-ECMO found significant elevations in inflammatory markers including interferon gamma (IFN-γ), IL-6, IL-1β, and TNF-α in children with abnormal head imaging (diffuse hypoxic injury, ICH, or ischemic stroke on ultrasound, CT or MRI) compared to children with normal head imaging. Additionally, IL-6 concentration was significantly elevated in children who did not survive their hospitalization compared to children who did, both on ECMO day 1 (median, 98.5 vs. 23.1 pg/ml) and at peak (median, 102.8 vs. 32.6 pg/ml) [41].

A prospective observational cohort study (n=266) on inflammatory cytokines in adults undergoing VV-ECMO found that higher inflammatory cytokines during ECMO were associated with a lower chance of survival, suggesting that increased inflammation during ECMO may be a potential prognostic biomarker [42]. This study also showed that levels of inflammatory cytokines including IL-6, IL-8, and TNF-α fell after discontinuing mechanical ventilation and switching to ECMO [42]. While mechanisms were not fully explored, patients undergoing mechanical ventilation with positive end-expiratory pressure (PEEP) ≥15 cm H_2O and/or driving pressures ≥ 19 cm H_2O prior to ECMO had higher inflammatory cytokine levels than those who had required lower PEEP and driving pressures [42]. Oncostatin M (OSM) is an inflammatory cytokine in the IL-6 family that is expressed in neurons, astrocytes, glia, and immune cells infiltrating the CNS, but also in non-neural tissue, such as lung and liver [43]. However, the role of OSM in ABI is controversial, with conflicting evidence. A prospective study of 29 VV-ECMO patients found that pre-decannulation OSM was elevated in VV-ECMO patients who did not survive compared to those who did (Mann-Whitney U-test: P=0.04) [43]. However, prior murine models have demonstrated that increased OSM expression is associated with improved neurological recovery following AIS, in contrast to the VV-ECMO study [44]. While studies of OSM after ABI have been contradictory, prior studies in lung injury have shown that OSM is released by infiltrating immune cells, with increased OSM serving as a marker of tissue injury [45]. However, given that OSM is not specific to neurological injury, and prior results have been conflicting, OSM may not be as useful compared to other brain-specific biomarkers that are discussed in this review.

Overall, inflammatory cytokines as an umbrella category are of variable utility as predictors of neurological injury in the setting of ECMO. Inflammatory cytokines such as IFN- γ , IL-6, IL-1β, and TNF-α have shown utility as an indicator of neurological complications in the pediatric ECMO population and as predictors of mortality in the adult population and require further study to establish reference ranges in the setting of various types of neurological injury. Conversely, OSM has shown conflicting results in various studies and lacks neurological specificity, and thus its utility in indicating neurological injury during ECMO may be limited.

POTENTIAL BRAIN-SPECIFIC BIOMARKERS FOR ECMO PATIENTS

Mitochondrial DNA

Mitochondrial DNA (mtDNA), sometimes referred to as circulating free mtDNA, fragments are released when cells are affected by mechanical or biological injury (as in hypoxia or inflammation) [46]. Physiologically, mtDNA appears to potentiate the immune response via toll-like receptors [46-48]. mtDNA levels have previously shown utility in predicting disease severity and mortality in critically ill patients with sepsis and acute lung injury [49,50].

In the setting of mechanical circulatory support, investigations into the role of mtDNA are limited. In a prospective study of 962 adult patients with post-cardiopulmonary bypass, mtDNA levels positively correlated with N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and Acute Physiology and Chronic Health Evaluation (APACHE) II score, an estimate of intensive care unit mortality risk [51]. In an ex vivo ECMO model that circulated heparinized human blood for 6 hours at differing flow rates, mtDNA was associated with loss in platelet function as measured by thrombelastography platelet mapping and collagen agonist stimulated responses [52]. mtDNA levels may have utility in predicting coagulation complications in ECMO patients, particularly in patients with ischemic and hemorrhagic strokes. In a single-center prospective study (n=100), mtDNA levels were significantly higher in patients with AIS compared to controls (P<0.05), positively correlated with clinical severity of stroke as determined by the National Institute of Health Stroke Scale, and that plasma mtDNA levels decreased with time after stroke (follow-up for up to 30 days, P<0.001) [53].

In summary, mtDNA is a promising biomarker specifically

for patients with coagulation complications in ECMO. Further research specifically in these cohorts across centers is necessary to validate these findings and determine accurate cutoffs.

Cell-Free DNA

Cell-free DNA (cfDNA) is a novel biomarker consisting of double-stranded DNA fragments released into the bloodstream under conditions of tissue stress resulting in cellular apoptosis or necrosis [54]. While cfDNA has been studied primarily in current literature in its application in liquid biopsy for oncological diagnosis and management, there has been a recent uptick in understanding the role that cfDNA may play in acute neurological conditions. In a prospective study of 54 patients with AIS, cfDNA was elevated in blood samples collected within 48 hours of AIS treated with IV thrombolysis compared to healthy controls [55]. Further, cfDNA levels on admission were able to discriminate between AIS and stroke mimics. An analysis of the plasma beta-globin gene allowed discrimination between AIS and ICH [55]. Similarly, in a prospective study of 54 Indian patients with AIS, cfDNA level was shown to correlate with poor neurological outcomes (measured by mRS score) at 3 months [56]. Additionally, in a prospective study of 60 patients admitted after acute ICH, higher plasma nuclear DNA levels at presentation correlated with poorer GCS scores [57]. Plasma cfDNA levels have also been shown to be predictive not only of worse functional outcomes, but also of stroke size at onset. In a prospective study of 88 patients presenting to the emergency department with stroke-like symptoms, plasma cfDNA taken within 3 hours of symptom onset correlated with ICH volume as measured by CT [58]. Although there are no studies using cfDNA in ECMO patients, given the utility of cfDNA in predicting stroke volume and severity, plasma cfDNA levels may be useful as an early indicator of possible stroke in ECMO patients.

Lipidomics and Metabolomics

Lipidomics and metabolomics offer a promising new avenue for markers of TBI, due to the increased permeability of the blood brain barrier (BBB) to lipids compared to proteins [59]. Cellular injury occurring after TBI carries with it a plethora of metabolic effects, resulting in derangements in processes such as oxidative phosphorylation and activation of phospholipase C and D, thereby triggering downstream signaling cascades. When the rat serum lipidome was analyzed 3 and 7 days after a controlled cortical TBI, lipidome panels achieved 85% accuracy at differentiating rats having undergone TBI from the control rats. Amongst lipids analyzed, polyunsaturated fatty acids (PUFAs), specifically free fatty acids, increased after TBI, while oxidized fatty acids decreased. Additionally, PUFA-esterified diacylglycerols increased, due to phospholipase signaling [59]. In further work by the same group, sensitivity of the lipidome panel exceeded 90% for lipidomic changes occurring within 24 hours following TBI. Sphingolipids, specifically sphingomyelins (SM), were increased as early as 4 hours following the injury, due to increased cell death. Additionally, ceramides were found to be increased, due to increased necroptosis [60].

In a metabolomic cohort study of 716 patients with TBI, carbohydrates derivatives including myoinositol, found in glial cells, were found to be elevated following TBI, which was postulated to be due to disruption of the BBB. Conversely, higher levels of phospholipids, including phosphatidylcholines, lysophosphatidylcholines, and SM, were correlated with decreased severity of TBI as well as improved functional outcomes [61]. Higher circulating levels of lysophospholipids were also found to be associated with improved outcomes in patients with mid TBI [62]. These results highlight the complex effects of circulating phospholipids and significant differences in the systemic response to ABI in humans compared with rodent models. Further research is needed to better characterize the functional consequences of altered lipid levels after ABI before they can be used effectively as clinical biomarkers.

While lipidomic and metabolomic changes have not yet been correlated to neurological complications of ECMO, the stability of lipids and their easier passage across the BBB make them promising candidates as biomarkers of ABI. Given the few numbers of studies, more work is needed in human subjects to characterize both lipidome and metabolome derangements, as well as their pathophysiology, prior to application in patients at risk for ABI including those on ECMO support. To fully assess the risk of ABI in patients on ECMO support, the integration of multi-omic data including metabolomics, proteomics, and genomics is recommended (Table 1).

CONCLUSIONS

Plasma biomarkers hold significant promise for the early detection and monitoring of ABI in ECMO patients. While research in other applications has been growing, there is limited data on biomarker applications in ECMO patients. The nascent stage of this research field, particularly in the context of ECMO, necessitates a comprehensive exploration and validation of these biomarkers. While some biomarkers like GFAP

Table 1. Summary of biomarkers promising for use in ECMO neuromonitoring

Serum biomarker	Physiology	Peak post-ABI and first elevation time	Previous use	Limitation
Tau	Cytoskeleton stabilization in unmyelinated axons in CNS	168 hr peak, elevation post 6 hr	Prediction of GCS following TBI, correlation with AIS severity	Studies examining utility in adult ECMO limited by sample size
GFAP	Astrocyte cytoskeletal integrity and astrogliosis	48–72 hr peak, increase after up to 2 hours	GFAP increased in pediatric ECMO patients who experienced brain injury.	Studies examining utility in adult ECMO limited by sample size
NfL	Axonal cytoskeleton component	Condition-dependent peak, increase in several hours after ABI	NfL increased after hypoxic brain injury in cardiac arrest, predictor of abnormal head CT in TBI.	Studies examining utility in adult ECMO limited by sample size
NSE	Paracrine regulator of glia and neurons expressed in astrocytes and oligodendrocytes	48 hr peak, increase in several hours	NSE is predictive of mortality and poor neurological outcomes in TBI.	Levels can be falsely elevated by the presence of hemolysis.
mt-DNA	Released upon cellular injury, promoting an inflammatory response	Within 6 hr, uncertain peak, but increase still present after 48 hr	Increased mt-DNA copy number in patients following both focal and diffuse TBI	No prior studies examining utility in ECMO
miRNA	Regulate cellular pathways, including those involved in neuronal repair	Peak 2–7 days after TBI	Specially selected miRNA profiles correlate with severity of ARDS in ECMO patients	No prior studies examining neurological injury prediction in ECMO
CfDNA	Double stranded DNA fragments released into the bloodstream during cellular apoptosis or necrosis	High inter-patient variability, 2 hr to 1 wk peak time	CfDNA levels have been shown to correlate with severity of TBI.	No prior studies examining neurological injury prediction in ECMO
Inflammatory cytokines	Small, secreted molecules controlling cell-cell interaction in the setting of inflammation regulation	Variable by cytokine	Elevations in pediatric ECMO population in those with head injury, elevations in adults associated with poor ECMO survival	No prior studies on neurological injury prediction in adult ECMO population
OSM	inflammatory cytokine in the IL-6 family that is expressed in neurons, astrocytes, glia, and immune cells	Biphasic peak	Elevated OSM associated with poor survival after VV-ECMO	Conflicting evidence: elevation associated with poor survival in VV-ECMO, improved recovery in murine model
Lipidomics/ metabolomics	Cellular injury results in derangements in processes such as oxidative phosphorylation	Variable by lipid/carbohydrate derivative	Lipidome panels achieved 85% accuracy at differentiating rats having undergone TBI from control rats.	No previous studies in ECMO

ECMO: extracorporeal membrane oxygenation; ABI: acute brain injury; CNS: central nervous system, GCS: Glasgow Coma Scale; TBI: traumatic brain injury; AIS: acute ischemic stroke; GFAP: glial fibrillary acidic protein; NfL: neurofilament light chain; CT: computed tomography; NSE: neuron-specific enolase; mt-DNA: mitochondrial DNA; miRNA: micro-RNA; ARDS: acute respiratory distress syndrome; CfDNA: cell-free DNA; OSM: Oncostatin M; IL: interleukin; VV: venovenous.

and NfL have shown promise, a vast array of other potential candidates remains unexplored in ECMO patients. Further research is needed to validate their clinical utility and to establish reliable biomarker panels tailored to specific patient populations and brain injury types. Future studies should focus on larger, well-defined ECMO cohorts (ECMO indications and cannulation strategy), understanding the dynamic kinetics and threshold for ECMO-associated ABI, and adopt standardized methodologies. By advancing our understanding of the complex interactions between brain injury, ECMO, and plasma biomarkers, clinicians will be better equipped to identify patients at risk, monitor their progress, and improve patient outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

SMC was supported by National Heart, Lung, and Blood Institute (1K23HL157610). AMG was supported by National Institute of Neurological Disorders and Stroke (5K23NS121628).

ACKNOWLEDGMENTS

None.

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Conceptualization: SK, SMC. Funding acquisition: SMC. Writing–original draft: all authors. Writing–review & editing: all authors.

REFERENCES

1. Lang NW, Schwihla I, Weihs V, Kasparek M, Joestl J, Hajdu S, et al. Survival rate and outcome of extracorporeal life support (ECLS) for treatment of acute cardiorespiratory failure in trauma patients. Sci Rep 2019;9:12902.
2. Migdady I, Rice C, Deshpande A, Hernandez AV, Price C, Whitman GJ, et al. Brain injury and neurologic outcome in patients undergoing extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care Med 2020;48:e611-9.
3. Cho SM, Ziai W, Mayasi Y, Gusdon AM, Creed J, Sharrock M, et al. Noninvasive neurological monitoring in extracorporeal membrane oxygenation. ASAIO J 2020;66:388-93.
4. Ong CS, Etchill E, Dong J, Shou BL, Shelley L, Giuliano K, et al. Neuromonitoring detects brain injury in patients receiving extracorporeal membrane oxygenation support. J Thorac Cardiovasc Surg 2023;165:2104-10.
5. Cho SM, Wilcox C, Keller S, Acton M, Rando H, Etchill E, et al. Assessing the SAfety and FEasibility of bedside portable low-field brain Magnetic Resonance Imaging in patients on ECMO (SAFE-MRI ECMO study): study protocol and first case series experience. Crit Care 2022;26:119.
6. Kim YJ, Kim YH, Youn CS, Cho IS, Kim SJ, Wee JH, et al. Different neuroprognostication thresholds of neuron-specific enolase in shockable and non-shockable out-of-hospital cardiac arrest: a prospective multicenter observational study in Korea (the KORHN-PRO registry). Crit Care 2023;27:313.
7. Gul SS, Huesgen KW, Wang KK, Mark K, Tyndall JA. Prognostic utility of neuroinjury biomarkers in post out-of-hospital cardiac arrest (OHCA) patient management. Med Hypotheses 2017;105:34-47.
8. Lee D, Cho Y, Ko Y, Heo NH, Kang HG, Han S. Neuron-specific enolase level as a predictor of neurological outcome in near-hanging patients: a retrospective multicenter study. PLoS One 2021;16:e0246898.
9. Bembea MM, Rizkalla N, Freedy J, Barasch N, Vaidya D, Pronovost PJ, et al. Plasma biomarkers of brain injury as diagnostic tools and outcome predictors after extracorporeal membrane oxygenation. Crit Care Med 2015;43:2202-11.
10. Floerchinger B, Philipp A, Camboni D, Foltan M, Lunz D, Lubnow M, et al. NSE serum levels in extracorporeal life support patients: relevance for neurological outcome? Resuscitation 2017;121:166-71.
11. Ramont L, Thoannes H, Volondat A, Chastang F, Millet MC, Maquart FX. Effects of hemolysis and storage condition on neuron-specific enolase (NSE) in cerebrospinal fluid and serum: implications in clinical practice. Clin Chem Lab Med 2005;43:1215-7.
12. Hol EM, Pekny M. Glial fibrillary acidic protein (GFAP) and the astrocyte intermediate filament system in diseases of the central nervous system. Curr Opin Cell Biol 2015;32:121-30.
13. Niebrój-Dobosz I, Rafałowska J, Lukasiuk M, Pfeffer A, Mossakowski MJ. Immunochemical analysis of some proteins in cerebrospinal fluid and serum of patients with ischemic strokes. Folia Neuropathol 1994;32:129-37.
14. Herrmann M, Vos P, Wunderlich MT, de Bruijn CH, Lamers KJ. Release of glial tissue-specific proteins after acute stroke: a comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein. Stroke 2000;31:2670-7.
15. Dvorak F, Haberer I, Sitzer M, Foerch C. Characterisation of the diagnostic window of serum glial fibrillary acidic protein for the differentiation of intracerebral haemorrhage and ischaemic stroke. Cerebrovasc Dis 2009;27:37-41.
16. Kaneko T, Kasaoka S, Miyauchi T, Fujita M, Oda Y, Tsuruta R, et al. Serum glial fibrillary acidic protein as a predictive biomarker of neurological outcome after cardiac arrest. Resuscitation 2009;80:790-4.
17. Hayashida H, Kaneko T, Kasaoka S, Oshima C, Miyauchi T, Fujita M, et al. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. Neurocrit Care 2010;12:252-7.
18. Wiesmann M, Steinmeier E, Magerkurth O, Linn J, Gottmann D, Missler U. Outcome prediction in traumatic brain injury: com-

parison of neurological status, CT findings, and blood levels of S100B and GFAP. Acta Neurol Scand 2010;121:178-85.
19. Pelinka LE, Kroepfl A, Schmidhammer R, Krenn M, Buchinger W, Redl H, et al. Glial fibrillary acidic protein in serum after traumatic brain injury and multiple trauma. J Trauma 2004;57:1006-12.
20. Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. J Neurotrauma 2004;21:1553-61.
21. Nylén K, Ost M, Csajbok LZ, Nilsson I, Blennow K, Nellgård B, et al. Increased serum-GFAP in patients with severe traumatic brain injury is related to outcome. J Neurol Sci 2006;240:85-91.
22. Fraser DD, Close TE, Rose KL, Ward R, Mehl M, Farrell C, et al. Severe traumatic brain injury in children elevates glial fibrillary acidic protein in cerebrospinal fluid and serum. Pediatr Crit Care Med 2011;12:319-24.
23. Amalia L. Glial fibrillary acidic protein (GFAP): neuroinflammation biomarker in acute ischemic stroke. J Inflamm Res 2021;14:7501-6.
24. Kapoor S, Ahmad SA, Muquit S, Gusdon A, Khanduja S, Ziai W, et al. Brain injury plasma biomarkers in patients on VA-ECMO: a pilot prospective observational study. Preprints.org [Preprint]. 2023 [cited 2023 Nov 20]. Available from: https://doi.org/10.20944/preprints202306.1266.v1
25. Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. Physiol Rev 2004;84:361-84.
26. Gao Y, Tan L, Yu JT, Tan L. Tau in Alzheimer's disease: mechanisms and therapeutic strategies. Curr Alzheimer Res 2018;15:283-300.
27. Zuckerman SL, Brett BL, Jeckell A, Yengo-Kahn AM, Solomon GS. Chronic traumatic encephalopathy and neurodegeneration in contact sports and American football. J Alzheimers Dis 2018;66:37-55.
28. Magnoni S, Esparza TJ, Conte V, Carbonara M, Carrabba G, Holtzman DM, et al. Tau elevations in the brain extracellular space correlate with reduced amyloid-β levels and predict adverse clinical outcomes after severe traumatic brain injury. Brain 2012;135(Pt 4):1268-80.
29. De Vos A, Bjerke M, Brouns R, De Roeck N, Jacobs D, Van den Abbeele L, et al. Neurogranin and tau in cerebrospinal fluid and plasma of patients with acute ischemic stroke. BMC Neurol 2017;17:170.
30. Mattsson N, Zetterberg H, Nielsen N, Blennow K, Dankiewicz J, Friberg H, et al. Serum tau and neurological outcome in cardiac arrest. Ann Neurol 2017;82:665-75.
31. Gabbita SP, Scheff SW, Menard RM, Roberts K, Fugaccia I, Zemlan FP. Cleaved-tau: a biomarker of neuronal damage after traumatic brain injury. J Neurotrauma 2005;22:83-94.
32. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry 2019;90:870-81.
33. Gafson AR, Barthélemy NR, Bomont P, Carare RO, Durham HD, Julien JP, et al. Neurofilaments: neurobiological foundations for biomarker applications. Brain 2020;143:1975-98.
34. Thebault S, Booth RA, Freedman MS. Blood neurofilament light chain: the neurologist's troponin? Biomedicines 2020;8:523.
35. Moseby-Knappe M, Mattsson N, Nielsen N, Zetterberg H, Blennow K, Dankiewicz J, et al. Serum neurofilament light chain for prognosis of outcome after cardiac arrest. JAMA Neurol 2019;76:64-71.
36. Wihersaari L, Reinikainen M, Furlan R, Mandelli A, Vaahersalo J, Kurola J, et al. Neurofilament light compared to neuron-specific enolase as a predictor of unfavourable outcome after out-of-hospital cardiac arrest. Resuscitation 2022;174:1-8.
37. Levin H, Lybeck A, Frigyesi A, Arctaedius I, Thorgeirsdóttir B, Annborn M, et al. Plasma neurofilament light is a predictor of neurological outcome 12 h after cardiac arrest. Crit Care 2023;27:74.
38. Martucci G, Arcadipane A, Tuzzolino F, Occhipinti G, Panarello G, Carcione C, et al. Identification of a circulating miRNA signature to stratify acute respiratory distress syndrome patients. J Pers Med 2020;11:15.
39. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45:27-37.
40. Datzmann T, Träger K. Extracorporeal membrane oxygenation and cytokine adsorption. J Thorac Dis 2018;10(Suppl 5):S653-60.
41. Caprarola SD, Ng DK, Carroll MK, Tekes A, Felling RJ, Salorio CF, et al. Pediatric ECMO: unfavorable outcomes are associated with inflammation and endothelial activation. Pediatr Res 2022;92:549-56.
42. Burrell AJC, Lubnow M, Enger TB, Nanjayya VB, Philipp A, Malfertheiner MV, et al. The impact of venovenous extracorporeal membrane oxygenation on cytokine levels in patients with severe acute respiratory distress syndrome: a prospective, observational study. Crit Care Resusc 2017;19(Suppl 1):37-44.
43. Setiadi H, El Banayosy AM, Koerner MM, Maybauer MO, Harper MD, Horstmanshof DA, et al. Oncostatin M as a biomarker to predict the outcome of VV ECMO supported patients with acute

pulmonary failure. J Heart Lung Transplant 2020;39(4 Supplement):S390.
44. Guo S, Li ZZ, Gong J, Xiang M, Zhang P, Zhao GN, et al. Oncostatin M confers neuroprotection against ischemic stroke. J Neurosci 2015;35:12047-62.
45. Knight D. Oncostatin M. In: Laurent GJ, Shapiro SD, editors. Encyclopedia of respiratory medicine. 2006; Academic Press. p. 254-8.
46. Harrington JS, Huh JW, Schenck EJ, Nakahira K, Siempos II, Choi AM. Circulating mitochondrial DNA as predictor of mortality in critically ill patients: a systematic review of clinical studies. Chest 2019;156:1120-36.
47. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 2012;36:401-14.
48. Nakahira K, Hisata S, Choi AM. The roles of mitochondrial damage-associated molecular patterns in diseases. Antioxid Redox Signal 2015;23:1329-50.
49. Mao JY, Li DK, Zhang HM, Wang XT, Liu DW. Plasma mitochondrial DNA levels are associated with acute lung injury and mortality in septic patients. BMC Pulm Med 2021;21:66.
50. Puskarich MA, Shapiro NI, Trzeciak S, Kline JA, Jones AE. Plasma levels of mitochondrial DNA in patients presenting to the emergency department with sepsis. Shock 2012;38:337-40.
51. Fan JX, Zeng L, Chen L, Li Y, Pu H, Shen J, et al. The hidden link between plasma mitochondrial DNA level and cardiac dysfunction after cardiopulmonary bypass. Research Square [Preprint]. 2020 [cited 2023 Nov 20]. Available from: https://doi.org/10.21203/rs.3.rs-36879/v1
52. Bynum J, Meyer A, Darlington DN, McIntosh C, Peltier G, Taylor AS, et al. Increased mitochondrial DNA in an ECMO model is associated with loss of platelet function. Blood 2017;130(Suppl 1):1126.
53. Tsai NW, Lin TK, Chen SD, Chang WN, Wang HC, Yang TM, et al. The value of serial plasma nuclear and mitochondrial DNA levels in patients with acute ischemic stroke. Clin Chim Acta 2011;412:476-9.
54. Corcoran RB, Chabner BA. Application of cell-free DNA analysis to cancer treatment. N Engl J Med 2018;379:1754-65.
55. Bustamante A, Mancha F, Macher HC, García-Berrocoso T, Giralt D, Ribó M, et al. Circulating cell-free DNA is a predictor of short-term neurological outcome in stroke patients treated with intravenous thrombolysis. J Circ Biomark 2016;5:1849454416668791.
56. Vajpeyee A, Wijatmiko T, Vajpeyee M, Taywade O, Pandey S, Chauhan PS. Clinical usefulness of cell-free DNA as a prognostic marker in acute ischemic stroke. Neurologist 2020;25:11-3.
57. Rainer TH, Wong LK, Lam W, Yuen E, Lam NY, Metreweli C, et al. Prognostic use of circulating plasma nucleic acid concentrations in patients with acute stroke. Clin Chem 2003;49:562-9.
58. Wang HC, Lin YJ, Lin WC, Ho JT, Chen WF, Chang WN, et al. The value of serial plasma nuclear and mitochondrial DNA levels in acute spontaneous intra-cerebral haemorrhage. Eur J Neurol 2012;19:1532-8.
59. Hogan SR, Phan JH, Alvarado-Velez M, Wang MD, Bellamkonda RV, Fernández FM, et al. Discovery of lipidome alterations following traumatic brain injury via high-resolution metabolomics. J Proteome Res 2018;17:2131-43.
60. Gier EC, Pulliam AN, Gaul DA, Moore SG, LaPlaca MC, Fernández FM. Lipidome alterations following mild traumatic brain injury in the rat. Metabolites 2022;12:150.
61. Thomas I, Dickens AM, Posti JP, Czeiter E, Duberg D, Sinioja T, et al. Serum metabolome associated with severity of acute traumatic brain injury. Nat Commun 2022;13:2545.
62. Gusdon AM, Savarraj JP, Redell JB, Paz A, Hinds S, Burkett A, et al. Lysophospholipids are associated with outcomes in hospitalized patients with mild traumatic brain injury. J Neurotrauma 2023 Oct 20 [Epub]. https://doi.org/10.1089/neu.2023.0046

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):399-408
https://doi.org/10.4266/acc.2023.01263

| pISSN 2586-6052 | eISSN 2586-6060

Abdominal compartment syndrome in critically ill patients

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Intra-abdominal hypertension can have severe consequences, including abdominal compartment syndrome, which can contribute to multi-organ failure. An increase in intra-abdominal hypertension is influenced by factors such as diminished abdominal wall compliance, increased intraluminal content, and certain systemic conditions. Regular measurement of intra-abdominal pressure is essential, and particular attention must be paid to patient positioning. Nonsurgical treatments, such as decompression of intraluminal content using a nasogastric tube, percutaneous drainage, and fluid balance optimization, play crucial roles. Additionally, point-of-care ultrasonography aids in the diagnosis and treatment of intra-abdominal hypertension. Emphasizing the importance of regular measurements, timely decompressive laparotomy is a definitive, but complex, treatment option. Balancing the urgency of surgical intervention against potential postoperative complications is challenging.

Key Words: abdominal compartment syndrome; critical care; intra-abdominal hypertension; multiple organ failure

Review Article

Received: September 27, 2023
Revised: November 10, 2023
Accepted: November 13, 2023

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INTRODUCTION

In critically ill patients, intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) frequently manifest as consequences of interventions such as intubation and fluid resuscitation. Notably, 25% of patients in intensive care units (ICUs) are affected by these conditions. Moreover, previous studies indicate that over half of these patients encounter IAH within the initial week of their ICU admission [1,2]. Under these circumstances, the timely diagnosis of IAH is crucial. If overlooked, IAH can evolve into ACS, which could subsequently result in organ dysfunction. This progression significantly affects the prognosis of critically ill patients. Reintam Blaser et al. [3] reported that during the initial 2 weeks of ICU admission, the presence and severity of IAH independently elevated both the 28- and 90-day mortality rates, with mortality surging to 38.6% when ACS manifested. Recognizing ACS early based on clinical indicators and risk factors can dramatically decrease the associated complications and mortality rates. Timely detection of these clinical signs allows for immediate emergency laparotomy to relieve the pressure. However, in practical clinical settings, measuring intra-abdominal pressure (IAP) in critically ill patients presents challenges. Although IAP's frequency has decreased, deterioration due to IAP still occurs in approximately 3%–5%

of patients [4].

In this review, we discuss the measurement of IAP, risk factors for IAH, and compartment syndrome. In 2013, the World Society of Abdominal Syndromes published the updated consensus definitions and clinical practice guidelines for IAH and ACS. Since then, IAH and ACS treatments have been developed and revised based on these guidelines. Based on these guidelines, we provide further insights into early detection, preventive therapeutic measures, and definitive treatments when these conditions manifest.

Search Strategy and Selection Criteria

Relevant articles were obtained through comprehensive searches of the Medline PubMed, Embase, and Cochrane Databases for the period ending 24 June, 2023. These databases were searched using keywords such as (Intra-abdominal pressure) OR (Intraabdominal pressure) OR IAP OR (Intra-abdominal hypertension) OR (Intraabdominal hypertension) OR IAH OR (abdominal compartment syndrome) OR ACS OR (intra-abdominal pressure measurement) OR (intraabdominal pressure measurement).

KEY MESSAGES

- Intra-abdominal hypertension can progress to critical abdominal compartment syndrome and significantly contribute to multi-organ failure.
- Close observation and an understanding of the factors that cause increased abdominal pressure are crucial.
- Regular intra-abdominal pressure measurements combined with timely assessment of potential organ failure are essential, emphasizing the importance of tailoring medical treatments and interventions.
- Balancing non-surgical treatments with the need for surgical intervention, particularly decompressive laparotomy, is a primary challenge in the care of patients at risk of intra-abdominal hypertension due to abdominal compartment syndrome.

PATHOPHYSIOLOGY

In individuals without pathological conditions, IAP is 0 mm Hg. During standard respiratory functions, positive pressure ventilation exerts a direct impact on IAP. Baseline IAP is 5 mm; but certain conditions, including coughing, obesity, and pregnancy, elevate the baseline. Notably, the factors that increase IAP can be categorized into five distinct groups: (1) Elasticity of abdominal wall and diaphragm (diminished abdominal wall compliance), (2) Increased intraluminal content, (3) Increased abdominal content, (4) Systemic condition causing capillary leak/fluid resuscitation, (5) Underlying causes.

The risk factors associated with each of these categories are detailed in Table 1. Compliance is forcibly restricted by mechanical ventilation, resulting in an IAP nearly double that of patients with spontaneous breathing [3]. Additionally, among the intra-abdominal organs, the movable wall area is confined to the abdominal wall and diaphragm [5]. The elasticity of abdominal lesions is notably reduced and compromised after surgical intervention [5-7] in which there is a reduction in the intra-abdominal volume domain, which could significantly influence its effects [8].

Within the intra-abdominal compartment, the viscera play a predominant role in influencing pressure dynamics. The dimensions of the bowel, coupled with the volume of its intraluminal content, can significantly affect pressure.

Interventions during resuscitation, particularly extensive fluid resuscitation, can cause capillary leakage. This, in conjunction with fluid resuscitation-induced systemic alterations, can contribute to an escalation in IAP [9,10]. Considering potential underlying etiologies is imperative. In patients presenting with elevated IAP attributable to underlying etiologies, there is an inherent predisposition toward the development of ACS.

DIAGNOSIS

Monitoring IAP is crucial for detecting the risk of ACS escalation. In patients undergoing treatment, early signs of IAH should be identified using IAP measurements before these signs manifest as organ failure or other symptoms. Although IAH grading is not an absolute criterion, higher IAH grades are associated with higher mortality rates [11]. In addition to IAP monitoring, early recognition of ACS through clinical signs and risk factors can significantly reduce the associated morbidity and mortality rates. Therefore, IAP monitoring is essential for ICU patients with risk factors.

MEASUREMENTS

Bladder pressure measurement is a straightforward and minimally invasive technique for reliably estimating IAP. This method relies on the principle that changes in IAP are reflected in intravesical pressure. As 90% of patients in the ICU are

equipped with a Foley catheter, this allows for convenient measurement directly during Foley insertion without the need for additional invasive procedures. The IAP is recorded in mm Hg. Care should be taken to avoid measurement during moments when IAP may acutely increase due to actions such as sneezing, laughing, shouting, coughing, or performing the Valsalva maneuver. Measurements should be made at the end of expiration with the patient in a supine position. The transducer needs to be zeroed at the level of the mid-axillary line, and the patient needs to be free from abdominal muscle contractions caused by conditions such as peritonitis (Figure 1) [12,13].

Understanding that the definition of ACS does not rely solely on the absolute values of IAP is crucial. Instead, the diagnosis of IAH should always be considered in conjunction with the potential for new organ dysfunction. Even if patients with IAH exhibit the same IAP levels, the risk of ACS can vary significantly owing to individual variables, such as blood pressure and abdominal wall compliance. Factors such as pregnancy, cirrhosis with ascites, and severe obesity can influence abdominal wall compliance, and consequently, the likelihood of ACS [12].

Abdominal perfusion pressure (APP) has been proposed as a more accurate predictive variable of visceral perfusion and a better endpoint for resuscitation than either IAP or mean arterial pressure alone. APP is the value obtained by subtracting IAP from mean arterial pressure (APP=mean arterial pressure–IAP). However, although there is evidence suggesting that APP may be a more accurate predictor of visceral perfusion and, potentially, a better endpoint for resuscitation than IAP or MAP alone, relevant randomized controlled trials or meta-analyses supporting this view conclusively are lacking. The observational studies available are predominantly of low quality due to bias and indirectness and mainly involve heterogeneous populations of ICU patients. These studies suggest that a reduced APP may be a poor independent prognostic

Table 1. Risk factors of IAH and ACS by category with associated references

Category	Risk factor	Reference
Elasticity of abdominal wall and diaphragm (diminished abdominal wall compliance)	Abdominal surgery	[14]
	Major trauma	[15]
	Major burns	[16]
	Prone positioning	[17]
	High PEEP	[18]
Increased intraluminal content	Gastroparesis/gastric distention	[19]
	Ileus	[20][a)]
	Colonic pseudo-obstruction	[21][a)]
	Volvulus	[22][a)]
Increased abdominal content	Acute pancreatitis	[23]
	Distended abdomen	[24]
	Hemoperitoneum/intra-peritoneal fluid collections	[25,26]
	Intra-abdominal infection/abscess	[27]
	Intra-abdominal or retroperitoneal mass	[28]
	Laparoscopy with excessive insufflation pressure	[29]
	Liver cirrhosis with ascites	[30]
	Peritoneal dialysis	[31]
Systemic condition due to capillary leak/fluid resuscitation	Acidosis	[11]
	Massive fluid resuscitation or massive transfusion	[32]
	Extracorporeal membrane oxygenation	[33]
	Sepsis	[34]
Underlying cause	Head elevation state in bed	[35]
	Obesity	[36]
	Peritonitis	[37]
	Pregnancy	[38]

IAH: intra-abdominal hypertension; ACS: abdominal compartment syndrome; PEEP: positive end-expiratory pressure.
a) References from case series.

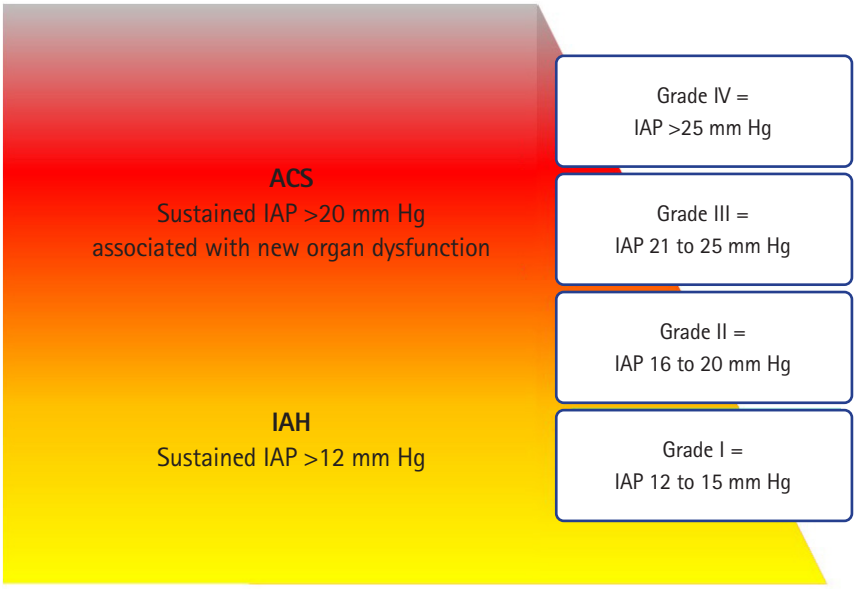

Figure 1. Intra-abdominal hypertension (IAH) grade definition. The red section in the figure indicates the potential range for the onset of abdominal compartment syndrome (ACS). As illustrated, ACS can manifest in any situation of IAH; however, the probability increases as the grade escalates [12].

factor, but the effects of interventions to improve APP on clinical outcomes are unclear. Therefore, the World Society of the Abdominal Compartment Syndrome (WSACS) withheld a recommendation on the use of APP in managing critically ill or injured patients until further high-quality interventional trials are conducted [12].

PRIMARY IAH OR ACS DEFINITIONS

Definitions of primary, secondary, and recurrent IAH or ACS are shown in Figure 2. These typically arise from direct abdominal trauma, abdominal surgery, mass-like lesions, or other causes of ascites. Secondary IAH or ACS originate from non-abdominal or non-pelvic sources, such as massive fluid resuscitation, major burns, or elevated IAP due to sepsis. Recurrent IAH or ACS refers to the re-emergence of elevated IAP after treatment in any given situation.

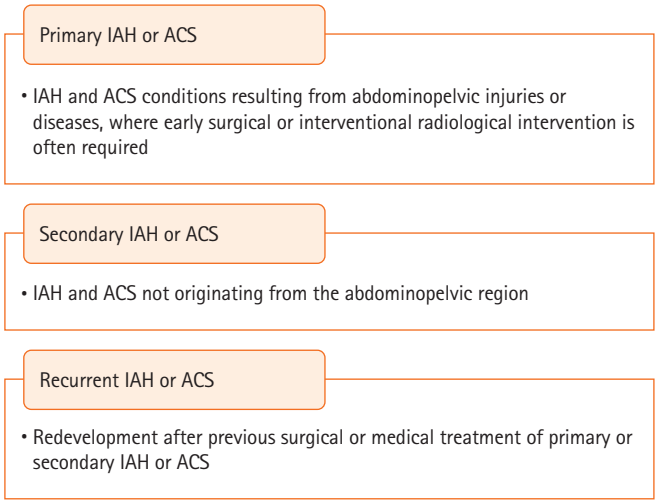

Figure 2. Intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS) definition from the consensus definitions of the 2013 World Society of the Abdominal Compartment Syndrome [12].

IAH ASSESSMENT: INFLUENCE OF RISK FACTORS

Although the causes of increased IAP can be categorized into four distinct groups, noting that elevated IAP is rarely caused by a single factor is important. Considering that multiple factors often interact in a complex manner, considering their multifaceted nature when developing treatment plans is essential. Risk factors and their corresponding references are detailed in Table 1 [14-38].

PROGRESSION OF IAH TO ACS AND ITS IMPACT ON VARIOUS ORGANS

An increase in IAP can lead to IAH and ACS, both of which can result in organ failure. This can manifest as both cause and consequence. Extensive research is currently underway to understand the far-reaching effects of elevated IAP. Isolated, transient elevation in IAP is seldom associated with significant organ failure in patients [39]. Persistent IAH can progress to organ failure. ACS is characterized by the onset of organ dysfunction due to a sustained increase in IAP. ICU patients with IAH commonly transition to multi-organ dysfunction not solely from elevated IAP, but also from other concurrent factors, such as sepsis. Therefore, monitoring IAP consistently to determine IAH persistence is essential. Distinguishing between organ dysfunction caused by IAH and that from other causes is crucial. Multi-organ dysfunction resulting from ACS progresses at an alarmingly rapid rate. However, the prompt resolution of ACS offers an opportunity to reverse these catastrophic outcomes [40]. In critically ill patients, rigorous and continuous monitoring of IAP is necessary to predict potential organ dysfunction attributable to IAH.

IMPACT ON THE KIDNEYS

Although ACS affects a multitude of organs, the kidneys are most often affected. This is largely because changes in kidney function are readily reflected as a decrease in urine output. Most initial treatments for acute kidney injury involve aggressive volume replacement, which significantly contributes to elevated IAP [41,42].

IMPACT ON THE RESPIRATORY SYSTEM

The respiratory system is also significantly affected. IAH induces a decrease in lung volume, which further impairs thoracic wall compliance [18]. Additionally, independent risk factors for ventilator-associated pneumonia were identified. Papakrivou et al. [43] found that the bacterial strains detected in patients with ventilator-associated pneumonia and IAH were predominantly intestinal flora, *Klebsiella*, *Proteus mirabilis*, and *Escherichia coli*. In contrast, in patients with ventilator-associated pneumonia and normal IAP, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Staphylococcus aureus* were mainly detected. This suggests the possibility of bacterial translocation in patients with IAH.

IMPACT ON CIRCULATION

IAH significantly affects hemodynamics. An increase in IAP elevates intrathoracic pressure and impedes venous return from the inferior vena cava. Additionally, an increase in abdominal pressure inherently increases afterload and results in a decrease in stroke volume. This leads to an increase in end-diastolic pressure, which, in turn, diminishes cardiac filling. The outcome is a reduction in systemic cardiac output, manifesting as decreased blood pressure and impaired circulation [44,45].

IMPACT ON INTRACRANIAL PRESSURE

IAH reduces the backflow of the venous plexus into the spinal canal. An increase in intrathoracic pressure elevates the central venous pressure, leading to diminished venous circulation through the jugular vein. This increases intracranial pressure [46,47].

IMPACT ON GASTROINTESTINAL TRACT AND HEPATOBILIARY SYSTEM

Functions of the intestine and liver are also affected by IAH. An increase in abdominal pressure directly affects the intestine, reducing splanchnic perfusion. Consequently, intestinal permeability increases, leading to mucosal barrier failure. This can trigger bacterial translocation, potentially causing organ failure [48]. Additionally, IAH leads to decreased gastrointestinal motility [49]. This reduced motility, both a cause and effect, can induce conditions such as ileus, which can further exacerbate IAH. Effects on the biliary system were also assessed. With the onset of IAH, there is a significant reduction in blood flow to the portal vein and inferior vena cava along with an increase in pressure. As a result of this sustained impact, cell damage and reparative responses can be observed in the liver [50,51]. While organ failures can occur individually, they often manifest in a multi-organ fashion [52].

TREATMENT AND MONITORING

Periodic measurement of IAP in patients at risk of ACS in the context of IAH is crucial. In addressing IAP monitoring for ICU patients, we suggest a strategy with nuances that account for the presence and number of risk factors related to IAH and ACS. The WSACS does not universally mandate IAP monitoring for all ICU patients but does stress its importance in those

with identifiable risk factors for IAH/ACS. The WSACS does recommend the use of the trans-bladder method for accurate IAP measurement and a protocolized approach to monitoring and management to enhance patient outcomes.

We recommend IAP monitoring for any ICU patient showing at least one known risk factor for IAH/ACS. This is based on the understanding that presence of a single risk factor significantly increases the risk of IAH/ACS, thus necessitating early and careful monitoring. Furthermore, in patients with two or more risk factors for IAH/ACS, we propose an enhanced level of IAP monitoring. This is due to the compounded risk from multiple factors and demands a more comprehensive monitoring strategy for prompt detection and effective intervention. This proactive approach is vital to reduce the incidence and impact of these conditions. Titration of medical treatments and interventions is of paramount importance (Figure 3).

The principle of this treatment is associated with five therapy categories that address factors that increase IAP. Recognizing patients in the early stages of low-grade IAH (i.e., grades I and II) allows for the prevention of and response to ACS through non-surgical treatments. However, regardless of the grade, the duration of IAH can directly affect a patient's prognosis, especially when IAH with organ failure occurs. Therefore, correction is crucial in such situations [39]. Close observation during these processes and the verification of organ failure are vital.

ELASTICITY OF ABDOMINAL WALL AND DIAPHRAGM (DIMINISHED ABDOMINAL WALL COMPLIANCE)

Appropriate sedation and analgesia may be beneficial for pain control. The efficacy of neuromuscular blockade in relation to the elasticity of the abdominal wall and diaphragm has been established [53]. However, continuous use of neuromuscular blockade is challenging. In De Laet's study [53], although neuromuscular blockade demonstrated a temporary reduction in IAP, definitive results in improving patient urine output or survival rates were not achieved. Therefore, neuromuscular blockade should be considered for treatment as a bridge to decompressive laparotomy. For patients with burns, escharotomy has been confirmed to improve the elasticity of the abdominal wall and alleviate ACS [54,55]. During treatment, this procedure should be considered alongside decompressive laparotomy.

INCREASED INTRALUMINAL AND ABDOMINAL CONTENT

In patients with underlying diseases or an increased volume of intraperitoneal fluid due to fluid therapy, temporary relief from elevated abdominal pressure can be provided through methods such as percutaneous drainage before resorting to resuscitative laparotomy [56]. From the initial stages of such

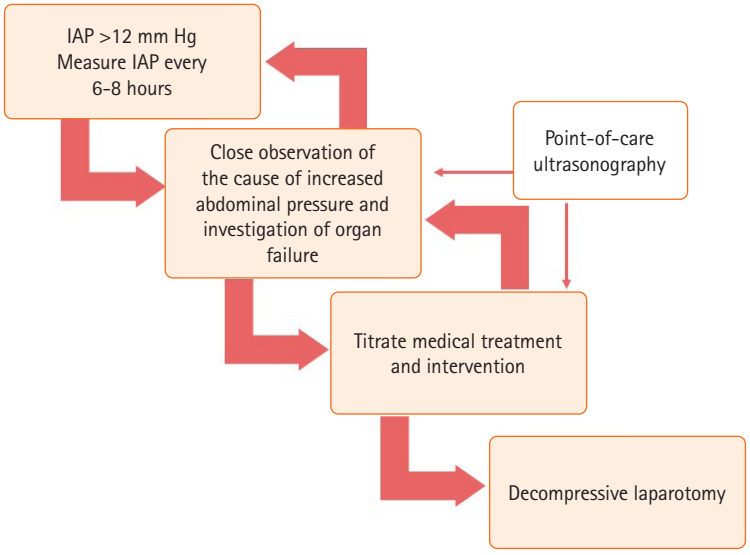

Figure 3. Management of intra-abdominal hypertension/abdominal compartment syndrome. IAP: intra-abdominal pressure.

non-invasive treatments, the recent addition of point-of-care ultrasonography to treat IAH is also crucial. The use of point-of-care ultrasonography for diagnostic and therapeutic approaches can be holistically applied to IAH treatment. Pereira et al. [36] used this for the initial treatment of patients with IAH/ACS. This procedure aided in adjusting the position of the nasogastric tube in the pyloric area to facilitate drainage and in assessing bowel movements and the need for further interventions, such as an enema. Percutaneous decompression can be considered by verifying the amount of intra-abdominal fluid (Figure 3).

SYSTEMIC CONDITION DUE TO CAPILLARY LEAK OR FLUID RESUSCITATION

By performing inferior vena cava and cardiac echography, the degree of fluid overload and cardiac function can be approached by adjusting the patient's fluid balance accordingly. The World Society of Abdominal Syndromes management algorithm recommends checking intraluminal contents, verifying the degree of abdominal wall compliance improvement, and confirming renal hepatic artery and portal-venous blood flow perfusion. Additionally, early veno-veno hemofiltration reduces IAP and diminishes the decline in organ function [57].

Cheatham et al. [35] demonstrated a significant elevation in IAP when subjects were in a supine position compared to a 30° head elevation. While the study did not elucidate the impact of these measurements on organ failure beyond a simple increase in values, the findings did indicate that measurements taken other than in the supine position might not reflect the true values accurately. This suggests that there may be a need to re-evaluate IAP measurements when the head is elevated. Furthermore, in IAH, the passive leg raising test, which is used to anticipate a patient's fluid response, can produce many false negatives. Therefore, verification and caution are needed when treating shock [58,59].

DECOMPRESSIVE LAPAROTOMY

When ACS occurs, the most definitive treatment method, decompressive laparotomy, must not be delayed. In such cases, an open abdomen may be a therapeutic option. Among the rescue therapy methods for an open abdomen, negative wound therapy, which is commonly implemented, has been reported to have minimal impact on IAP measurements [60]. Although surgical intervention remains the definitive solution for certain clinical conditions, many patients may not be hemodynamically stable for immediate surgery. The rapid restoration of systemic perfusion following open abdominal procedures is essential. However, prolonged maintenance of an open abdomen can lead to postoperative complications.

Furthermore, the resuscitation phase after open surgery does not always lead to immediate recovery. There may be instances in which extensive fluid resuscitation is required for a certain period, leading to deliberations regarding the timing of abdominal closure. Nonetheless, once the primary treatment goal is accomplished, prompt closure of the abdominal wall (including the fascia) should be attempted because of the potential complications and increased difficulty of future closures. However, care is needed as forcing fascial closure can increase the risk of ACS recurrence. In some cases, the abdomen may close while the fascia is excluded. This can lead to herniation. Alternatively, subsequent surgery may be required. This could involve applying a mesh or separation and suturing of the abdominal fascia along the midline to reconstruct the abdominal wall [61].

CONCLUSIONS

IAH presents multifaceted challenges in patient care and has the potential to progress to life-threatening ACS. Regular monitoring of IAP, interventions aided by point-of-care ultrasonography, and timely decompressive laparotomy are pivotal for mitigating the associated risks and ensuring optimal patient outcomes.

CONFLICT OF INTEREST

Dowan Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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REFERENCES

1. Malbrain ML, Chiumello D, Cesana BM, Reintam Blaser A, Starkopf J, Sugrue M, et al. A systematic review and individual patient data meta-analysis on intra-abdominal hypertension in critically ill patients: the wake-up project. World initiative on Abdominal Hypertension Epidemiology, a Unifying Project (WAKE-Up!). Minerva Anestesiol 2014;80:293-306.
2. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med 2005;33:315-22.
3. Reintam Blaser A, Regli A, De Keulenaer B, Kimball EJ, Starkopf L, Davis WA, et al. Incidence, risk factors, and outcomes of intra-abdominal hypertension in critically ill patients: a prospective multicenter study (IROI Study). Crit Care Med 2019;47:535-42.
4. Malbrain ML, Deeren D, De Potter TJ. Intra-abdominal hypertension in the critically ill: it is time to pay attention. Curr Opin Crit Care 2005;11:156-71.
5. Vlot J, Wijnen R, Stolker RJ, Bax KN. Optimizing working space in laparoscopy: CT measurement of the effect of pre-stretching of the abdominal wall in a porcine model. Surg Endosc 2014;28:841-6.
6. Malbrain ML, Peeters Y, Wise R. The neglected role of abdominal compliance in organ-organ interactions. Crit Care 2016;20:67.
7. Song C, Alijani A, Frank T, Hanna GB, Cuschieri A. Mechanical properties of the human abdominal wall measured in vivo during insufflation for laparoscopic surgery. Surg Endosc 2006;20:987-90.
8. Petro CC, Raigani S, Fayezizadeh M, Rowbottom JR, Klick JC, Prabhu AS, et al. Permissible intraabdominal hypertension following complex abdominal wall reconstruction. Plast Reconstr Surg 2015;136:868-81.
9. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg 2003;138:637-43.
10. Kelm DJ, Perrin JT, Cartin-Ceba R, Gajic O, Schenck L, Kennedy CC. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock 2015;43:68-73.
11. Vidal MG, Ruiz Weisser J, Gonzalez F, Toro MA, Loudet C, Balasini C, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. Crit Care Med 2008;36:1823-31.
12. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 2013;39:1190-206.
13. Kirkpatrick AW, Sugrue M, McKee JL, Pereira BM, Roberts DJ, De Waele JJ, et al. Update from the Abdominal Compartment Society (WSACS) on intra-abdominal hypertension and abdominal compartment syndrome: past, present, and future beyond Banff 2017. Anaesthesiol Intensive Ther 2017;49:83-7.
14. Ersryd S, Gidlund KD, Wanhainen A, Smith L, Björck M. Editor's choice: abdominal compartment syndrome after surgery for abdominal aortic aneurysm: subgroups, risk factors, and outcome. Eur J Vasc Endovasc Surg 2019;58:671-9.
15. He L, Yi C, Hou Z, Hak DJ. Intraabdominal hypertension/abdominal compartment syndrome after pelvic fractures: How they occur and what can be done? Injury 2019;50:919-25.
16. Struck MF, Reske AW, Schmidt T, Hilbert P, Steen M, Wrigge H. Respiratory functions of burn patients undergoing decompressive laparotomy due to secondary abdominal compartment syndrome. Burns 2014;40:120-6.
17. Yi M, Leng Y, Bai Y, Yao G, Zhu X. The evaluation of the effect of body positioning on intra-abdominal pressure measurement and the effect of intra-abdominal pressure at different body positioning on organ function and prognosis in critically ill patients. J Crit Care 2012;27:222.

18. Regli A, Pelosi P, Malbrain ML. Ventilation in patients with intra-abdominal hypertension: what every critical care physician needs to know. Ann Intensive Care 2019;9:52.
19. Parkman HP, Hasler WL, Fisher RS; American Gastroenterological Association. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004;127:1592-622.
20. Madl C, Druml W. Gastrointestinal disorders of the critically ill. Systemic consequences of ileus. Best Pract Res Clin Gastroenterol 2003;17:445-56.
21. Granero Castro P, Fernández Arias S, Moreno Gijón M, Alvarez Martínez P, Granero Trancón J, Álvarez Pérez JA, et al. Emergency surgery in chronic intestinal pseudo-obstruction due to mitochondrial neurogastrointestinal encephalomyopathy: case reports. Int Arch Med 2010;3:35.
22. Marin AC, Hechter S, Prasad A, Alnabwani D, Lwoodsky C, Cheriyath P. Abdominal compartment syndrome (ACS) with sigmoid volvulus (SV): lost hours are lost lives. Cureus 2023;15:e33741.
23. Marcos-Neira P, Zubia-Olaskoaga F, López-Cuenca S, Bordejé-Laguna L; Epidemiology of Acute Pancreatitis in Intensive Care Medicine study group. Relationship between intra-abdominal hypertension, outcome and the revised Atlanta and determinant-based classifications in acute pancreatitis. BJS Open 2018;1:175-81.
24. Bouveresse S, Piton G, Badet N, Besch G, Pili-Floury S, Delabrousse E. Abdominal compartment syndrome and intra-abdominal hypertension in critically ill patients: diagnostic value of computed tomography. Eur Radiol 2019;29:3839-46.
25. Singh AK, Samanta J, Dawra S, Gupta P, Rana A, Sharma V, et al. Reduction of intra-abdominal pressure after percutaneous catheter drainage of pancreatic fluid collection predicts survival. Pancreatology 2020;20:772-7.
26. Battey TW, Dreizin D, Bodanapally UK, Wnorowski A, Issa G, Iacco A, et al. A comparison of segmented abdominopelvic fluid volumes with conventional CT signs of abdominal compartment syndrome in a trauma population. Abdom Radiol (NY) 2019;44:2648-55.
27. Murphy PB, Parry NG, Sela N, Leslie K, Vogt K, Ball I. Intra-abdominal hypertension is more common than previously thought: a prospective study in a mixed medical-surgical ICU. Crit Care Med 2018;46:958-64.
28. Daliakopoulos SI, Schaedel M, Klimatsidas MN, Spiliopoulos S, Koerfer R, Tenderich G. Intra-abdominal hypertension due to heparin-induced retroperitoneal hematoma in patients with ventricle assist devices: report of four cases and review of the literature. J Cardiothorac Surg 2010;5:108.
29. Raval AD, Deshpande S, Koufopoulou M, Rabar S, Neupane B, Iheanacho I, et al. The impact of intra-abdominal pressure on perioperative outcomes in laparoscopic cholecystectomy: a systematic review and network meta-analysis of randomized controlled trials. Surg Endosc 2020;34:2878-90.
30. Pereira R, Buglevski M, Perdigoto R, Marcelino P, Saliba F, Blot S, et al. Intra-abdominal hypertension and abdominal compartment syndrome in the critically ill liver cirrhotic patient-prevalence and clinical outcomes: a multicentric retrospective cohort study in intensive care. PLoS One 2021;16:e0251498.
31. Castellanos LB, Clemente EP, Cabañas CB, Parra DM, Contador MB, Morera JC, et al. Clinical relevance of intraperitoneal pressure in peritoneal dialysis patients. Perit Dial Int 2017;37:562-7.
32. Dalfino L, Tullo L, Donadio I, Malcangi V, Brienza N. Intra-abdominal hypertension and acute renal failure in critically ill patients. Intensive Care Med 2008;34:707-13.
33. Glowka TR, Schewe JC, Muenster S, Putensen C, Kalff JC, Pantelis D. Decompressive laparotomy for the treatment of the abdominal compartment syndrome during extracorporeal membrane oxygenation support. J Crit Care 2018;47:274-9.
34. Pereira B, Dorigatti A, Melek M, Dos Santos J, Ferreira M, Calderan T, et al. Septic shock patients admitted to the intensive care unit with higher SOFA score tend to have higher incidence of abdominal compartment syndrome: a preliminary analysis. Anaesthesiol Intensive Ther 2019;51:370-2.
35. Cheatham ML, De Waele JJ, De Laet I, De Keulenaer B, Widder S, Kirkpatrick AW, et al. The impact of body position on intra-abdominal pressure measurement: a multicenter analysis. Crit Care Med 2009;37:2187-90.
36. Pereira BM, Pereira RG, Wise R, Sugrue G, Zakrison TL, Dorigatti AE, et al. The role of point-of-care ultrasound in intra-abdominal hypertension management. Anaesthesiol Intensive Ther 2017;49:373-81.
37. Basu A, Pai DR. Early elevation of intra-abdominal pressure after laparotomy for secondary peritonitis: a predictor of relaparotomy? World J Surg 2008;32:1851-6.
38. Chun R, Kirkpatrick AW. Intra-abdominal pressure, intra-abdominal hypertension, and pregnancy: a review. Ann Intensive Care 2012;2 Suppl 1:S5.
39. Kyoung KH, Hong SK. The duration of intra-abdominal hypertension strongly predicts outcomes for the critically ill surgical patients: a prospective observational study. World J Emerg Surg 2015;10:22.
40. De Waele JJ, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal hypertension and abdominal compartment syndrome. Am

J Kidney Dis 2011;57:159-69.
41. Smit M, Hofker HS, Leuvenink HG, Krikke C, Jongman RM, Zijlstra JG, et al. A human model of intra-abdominal hypertension: even slightly elevated pressures lead to increased acute systemic inflammation and signs of acute kidney injury. Crit Care 2013;17:425.
42. Mohmand H, Goldfarb S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. J Am Soc Nephrol 2011;22:615-21.
43. Papakrivou E, Makris D, Manoulakas E, Karvouniaris M, Zakynthinos E. Intra-abdominal hypertension is a risk factor for increased VAP incidence: a prospective cohort study in the ICU of a tertiary hospital. J Intensive Care Med 2020;35:700-7.
44. Malbrain ML, De Waele JJ, De Keulenaer BL. What every ICU clinician needs to know about the cardiovascular effects caused by abdominal hypertension. Anaesthesiol Intensive Ther 2015;47:388-99.
45. Ridings PC, Bloomfield GL, Blocher CR, Sugerman HJ. Cardiopulmonary effects of raised intra-abdominal pressure before and after intravascular volume expansion. J Trauma 1995;39:1071-5.
46. Citerio G, Vascotto E, Villa F, Celotti S, Pesenti A. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. Crit Care Med 2001;29:1466-71.
47. Montorfano L, Giambartolomei G, Funes DR, Lo Menzo E, Dip F, White KP, et al. The Cushing reflex and the vasopressin-mediated hemodynamic response to increased intracranial pressure during acute elevations in intraabdominal pressure. Surgery 2020;167:478-83.
48. Diebel LN, Dulchavsky SA, Brown WJ. Splanchnic ischemia and bacterial translocation in the abdominal compartment syndrome. J Trauma 1997;43:852-5.
49. Khripun AI, Ettinger AP, Chadaev AP, Tat'kov SS. Changes in the contractile and bioelectrical activities of the rat small intestine under increased intra-abdominal pressure. Izv Akad Nauk Ser Biol 1997;596-602.
50. Mogilner JG, Bitterman H, Hayari L, Brod V, Coran AG, Shaoul R, et al. Effect of elevated intra-abdominal pressure and hyperoxia on portal vein blood flow, hepatocyte proliferation and apoptosis in a rat model. Eur J Pediatr Surg 2008;18:380-6.
51. Antoniou EA, Kairi E, Margonis GA, Andreatos N, Sasaki K, Damaskos C, et al. Effect of increased intra-abdominal pressure on liver histology and hemodynamics: an experimental study. In Vivo 2018;32:85-91.
52. Malbrain ML, Roberts DJ, Sugrue M, De Keulenaer BL, Ivatury R, Pelosi P, et al. The polycompartment syndrome: a concise state-of-the-art review. Anaesthesiol Intensive Ther 2014;46:433-50.
53. De Laet I, Hoste E, Verholen E, De Waele JJ. The effect of neuromuscular blockers in patients with intra-abdominal hypertension. Intensive Care Med 2007;33:1811-4.
54. Oda J, Ueyama M, Yamashita K, Inoue T, Harunari N, Ode Y, et al. Effects of escharotomy as abdominal decompression on cardiopulmonary function and visceral perfusion in abdominal compartment syndrome with burn patients. J Trauma 2005;59:369-74.
55. Butts CC, Holmes JH, Carter JE. Surgical escharotomy and decompressive therapies in burns. J Burn Care Res 2020;41:263-9.
56. Parra MW, Al-Khayat H, Smith HG, Cheatham ML. Paracentesis for resuscitation-induced abdominal compartment syndrome: an alternative to decompressive laparotomy in the burn patient. J Trauma 2006;60:1119-21.
57. Xu JM, Yang HD, Tian XP. Effects of early hemofiltration on organ function and intra-abdominal pressure in severe acute pancreatitis patients with abdominal compartment syndrome. Clin Nephrol 2019;92:243-9.
58. Mahjoub Y, Touzeau J, Airapetian N, Lorne E, Hijazi M, Zogheib E, et al. The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension. Crit Care Med 2010;38:1824-9.
59. Beurton A, Teboul JL, Girotto V, Galarza L, Anguel N, Richard C, et al. Intra-abdominal hypertension is responsible for false negatives to the passive leg raising test. Crit Care Med 2019;47:e639-47.
60. García AF, Sánchez ÁI, Gutiérrez ÁJ, Bayona JG, Naranjo MP, Lago S, et al. Effect of abdominal negative-pressure wound therapy on the measurement of intra-abdominal pressure. J Surg Res 2018;227:112-8.
61. Patel NY, Cogbill TH, Kallies KJ, Mathiason MA. Temporary abdominal closure: long-term outcomes. J Trauma 2011;70:769-74.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):409-424
https://doi.org/10.4266/acc.2023.00703

| pISSN 2586-6052 | eISSN 2586-6060

Early detection and assessment of intensive care unit–acquired weakness: a comprehensive review

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Intensive care unit-acquired weakness (ICU-AW) is a serious complication in critically ill patients. Therefore, timely and accurate diagnosis and monitoring of ICU-AW are crucial for effectively preventing its associated morbidity and mortality. This article provides a comprehensive review of ICU-AW, focusing on the different methods used for its diagnosis and monitoring. Additionally, it highlights the role of bedside ultrasound in muscle assessment and early detection of ICU-AW. Furthermore, the article explores potential strategies for preventing ICU-AW. Healthcare providers who manage critically ill patients utilize diagnostic approaches such as physical exams, imaging, and assessment tools to identify ICU-AW. However, each method has its own limitations. The diagnosis of ICU-AW needs improvement due to the lack of a consensus on the appropriate approach for its detection. Nevertheless, bedside ultrasound has proven to be the most reliable and cost-effective tool for muscle assessment in the ICU. Combining the Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score assessment, and ultrasound can be a convenient approach for the early detection of ICU-AW. This approach can facilitate timely intervention and prevent catastrophic consequences. However, further studies are needed to strengthen the evidence.

Key Words: computed tomography; critical illness; diagnosis; intensive care units; muscle weakness; ultrasound

Review Article

Received: May 14, 2023
Revised: October 4, 2023
Accepted: October 17, 2023

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INTRODUCTION

Skeletal muscle dysfunction is a common issue in intensive care units (ICUs), which can result from ICU admission or be the underlying cause. Muscle weakness and loss of function are common manifestations of this condition [1]. The history of this condition dates to Hippocrates, who described “spontaneous lassitude" and muscle atrophy in patients dying from infection and cancer [2]. Osler also observed weakness in critical illness early [3]. In 1977, a status asthmaticus patient who received greater doses of hydrocortisone and concurrent neuromuscular inhibition was reported to have developed myopathy [4]. Since then, Bolton and his colleagues have conducted significant research on ICU patients with polyneuropathy [5]. In the past 20 years, advances in post-ICU survival have led to a deeper understanding of frailty acquired in the ICU. Healthcare professionals, patients, and families are all aware of the

severity of neuromuscular damage in the growing number of patients receiving post-ICU rehabilitation [6]. ICU-Acquired Weakness (ICU-AW) is defined as the weakness and inability to move against resistance in critically ill patients, manifesting as widespread and symmetrical weakness affecting both the extremities and the respiratory muscles following the onset of a severe medical condition, with no discernible underlying cause other than the critical illness itself along with Medical Research Council (MRC) sum score of less than 48/60 or Dominant-hand grip dynamometry scores of less than 11 kg (interquartile range [IQR], 10–40 kg) in males and less than 7 kg (IQR, 0–7.3 kg) in females [2,7]. Healthcare professionals need to know when to suspect ICU-AW, what risk factors to identify, how to diagnose it, what the prognosis is, and how to improve recovery to lower the prevalence of the disorder. [6].

KEY MESSAGES

- Intensive care unit-acquired weakness (ICU-AW) is a common and potentially life-threatening complication in critically ill patients, and early detection is crucial for timely intervention.
- Bedside ultrasound is the most reliable and cost-effective tool for muscle assessment and detection of ICU-AW, and a combination of Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II scores with ultrasound can be a convenient approach for early detection and monitoring of ICU-AW.
- As there is no treatment, prevention of ICU-AW is so important and can be achieved through early mobility, avoiding hyperglycemia, optimizing nutrition, and minimizing sedation.

METHODS

To ensure a thorough and reliable literature review, various steps were taken. Initially, an extensive search was conducted on peer-reviewed journals using a diverse set of keywords such as "bioimpedance," "computed tomography," "dual-energy X-ray absorptiometry," "intensive care unit-acquired weakness," "muscle assessment," and "ultrasound." The search was limited to peer-reviewed journals and excluded conference papers or reports. Two databases, namely PubMed and Google Scholar were used for the search. Additionally, the reference section of each identified article was examined to find more relevant articles. The search included articles published between 2000 and 2022.

EPIDEMIOLOGY

ICUs globally care for 13–20 million patients annually [8], with ICU-AW occurring in 25%–31% of medical and 57%–74% of surgical ICUs [9]. The Incidence varies by patient characteristics [10], and can develop rapidly, even within hours of admission or mechanical ventilation [11-13], ICU-AW can persist for years, especially in patients ventilated for over 4–7 days, and is common in elderly patients (up to 70%) [1,14].

CLASSIFICATION

ICU-AW can impact the entire neuromuscular system, causing critical illness polyneuropathy (CIP) in the peripheral nerves, critical illness myopathy (CIM) in the muscle, or critical illness neuromyopathy (CINMB), which is a combination of both. These conditions can result in symmetrical weakness and atrophy of the muscles, with CIP primarily affecting lower limbs. In contrast, CIM acts the proximal areas and can lead to respiratory muscle weakness, and descriptions of CINMB have been observed to be transient with flaccid areflexic weakness affecting all four limbs, facial and ocular muscles without sensory impairment, occurring 2 to 10 days after discontinuing non-depolarizing neuromuscular blocking agents [6,7,15]. However, muscle weakness, called ICU-AW, more frequently appears as a secondary problem while patients receive treatment for more serious illnesses. ICU-AW is clinically detectable in critically ill patients without a plausible explanation. These conditions could significantly impact long-term patient outcomes if not addressed [6].

RISK FACTORS

There are many risk factors (Figure 1), including that ICU-AW is strongly linked with continuous APACHE II scores ≥15. Additionally, corticosteroids, aminoglycosides, and neuromuscular blocking agents have been demonstrated to be significantly associated with ICU-AW [16]. Although there is no significant association between Sequential Organ Failure Assessment (SOFA) and ICU-AW, the SOFA score is >7, the first-week total SOFA score is >45, the duration of dysfunction in two organs, and neurologic failure appeared to be independent risk variables for ICU-AW in every single research [17]. Individuals

Figure 1. Pathophysiology, risk factors, and consequences of intensive care unit-acquired weakness (ICU-AW). ADLS: activity of daily livings; TNF: tumor necrosis factor; IL: interleukin.
a) Drugs: like vasoactive medication as B-Blockers (+), corticosteroids (±), neuromuscular blocking agents (–) combined with corticosteroids infused for more than 48 hours (+), certain antibiotics as clindamycin, erythromycin, quinolones, polymyxin, tetracycline and vancomycin which act on neuromuscular junction but not proven to be the sole cause for ICU-AW (±).

with sepsis were more vulnerable to muscle weakness caused by sepsis-induced myopathy or axonal neuropathy [18]. Pro-inflammatory cytokines have been identified to control muscle mass, so it is important to control sepsis early [19]. It was concluded that no significant association existed between days of norepinephrine administration and ICU-AW [20]. But treatment with norepinephrine was found to be a substantial risk for developing ICU-AW in the single study on multivariable analysis [21]. Several other risk factors were presented, including the female sex, as women were more vulnerable than men, possibly because of their less muscle mass. In every study, hyperosmolarity, hyperglycemia, high lactate, and duration of mechanical ventilation and parenteral nutrition were associated with an increased risk of developing ICU-AW [16].

PATHOPHYSIOLOGY

ICU-AW pathogenesis still needs to be better understood. Two main factors contribute to this condition: decreased muscle mass and reduced muscle function. In critical illness, muscle mass loss occurs due to a reduction in protein production and an increase in protein degradation by the ubiquitin-proteasome system. This catabolic state is characterized by decreased anabolic hormone effect, increased catabolic hormones, and immobilization, all contributing to muscle wasting [17]. Structural muscle changes, such as inflammation or necrosis, substantial infiltration of muscle with adipose tissue, and fibrosis, are commonly observed in severely ill individuals [22]. Microcirculatory disturbances can also jeopardize oxygen supply and perfusion, leading to chronic membrane depolarization of terminal motor axons, neuronal damage, and axonal degeneration [23,24].

Bioenergetic failure caused by cellular damage worsened by inflammation, hyperglycemia, and free radical damage can compromise mitochondrial energy synthesis. Dysfunctional mitochondria generate reactive oxygen species and free radicals, leading to a macromolecular and organelle damage cycle [24]. Impaired autophagy activation during acute disease allows damage to accumulate to mitochondria and other cellular components, leading to degenerative alterations that impair muscle function [22,24-26]. The inactivation of sodium channels in neuronal and muscle cell membranes leads to reversible hypo- or inexcitability. Altered excitation-contraction coupling and intracellular calcium homeostasis contribute to reduced muscle contractility [24].

Recent research suggests that failure of coordinated repeated firing within motor neurons may occur early, involving the central nervous system. This failure may occur before the electrical breakdown of axons and nerve-muscle coupling [27]. Muscle inactivity during ICU stays leads to a rapid decline in protein synthesis and proteolysis in respiratory and limb muscles, indicating early disturbances in proteostasis (Figure 1). These effects are independent of muscle function or type, emphasizing the need for therapeutic interventions to prevent skeletal muscle wasting in critical care patients. Studies show that anabolic signaling and protein synthesis decrease rapidly while key proteolytic systems activate during ICU care [28].

SHORT AND LONG-TERM CONSEQUENCES

ICU-AW can cause a variety of short- and long-term negative effects (Figure 1).

Short-Term Consequences

A higher risk of ICU death has been independently linked to the onset and severity of ICU-AW, which has been linked to limb muscle loss. Although not conclusive, it has also been seen in diaphragm malfunction [29]. Additionally, it has been discovered that respiratory muscle and limb weakness are separate predictors of a protracted need for artificial ventilation [30]. Elevated extubation failure rates in medical patients were independently correlated with limb muscular weakness [31]. Reintubation was required in 50% of them after extubation failed; of them, 50% died in the ICU. Additionally, muscle weakness is linked to longer ICU and hospital stays and costs [29]. Furthermore, neuromuscular weakening has been cited as a major factor causing ICU-acquired swallowing difficulties, such as post-extubation dysphagia [32]. Effective coughing may be hampered by abdominal muscular weakness [15]. More patients were sent to rehabilitation facilities, and worse short-term results were linked to ICU-acquired frailty.

Long-Term Consequences

The survivors of critical illnesses have a higher chance of dying later in life [26,33], which is exacerbated in patients suffering from ICU-acquired frailty. A lower compound muscle action potential on ICU day 8, regardless of clinical weakness identified by the MRC total score [34], and respiratory muscle weakness demonstrated by a low maximal inspiratory pressure field [35] was also independently associated with greater 1-year mortality. A 5-year survival rate is also linked to a low (MRC sum score of 48) at hospital discharge [36]. Five years follow-

ing ICU admission, a diverse sample of patients with critical illness demonstrated decreased physical quality of life, significantly shortened 6-minute walking distance (6-MWD), and lower handgrip force [33]. A significant independent predictor for long-term weakness, various illnesses, and poor quality of life after ICU discharge appeared to be the development of weakness [37]. A myogenic origin of ICU-AW seemed to have a more favorable outcome in nearly full recovery than a neurogenic origin, which left 50 to 75% of patients with persisting weakness or even tetraparesis [29,38].

DETECTION OF ICU-AW

The consensus across various studies is that early identification of ICU-AW is important in its prevention. However, there is no precise designated day for such assessments. Based on consensus, patients who remain in the ICU beyond the 8th day from admission, referred to as "long-stay patients," undergo a systematic evaluation to assess awakening and cooperation. So, it is preferred that as soon as admission to ICU, we start with SOFA and APACHE screening accompanied by an ultrasound assessment in the first week is the most beneficial approach [11,39]. Early detection, diagnosis, and successful prevention are crucial measures to reduce ICU-AW incidence, given the absence of an effective treatment for this condition. The importance of timely identification and management of ICU-AW must be considered [40]. A cross-sectional survey study conducted in 2021 focused on assessing ICU-AW in some low-income countries; insufficient diagnosis and early identification of ICU-AW are common due to staff-related, patient-related, and management-related factors. Staff obstacles include limited understanding, lack of guidelines for high-risk patients, and low priority for ICU-AW. Patient-related barriers involve cognitive decline, inability to participate, unconsciousness, and excessive sedation. Management-related challenges are perceived as low priority and inadequate staffing for ICU-AW assessment. However, achieving a clinical diagnosis, performing appropriate testing, and maintaining clear communication with patients and ICU colleagues is crucial [14]. This study also found that the MRC scores (79%), Manual Muscle Tests scale (73%), and electrophysiological assessments (70%) were the top three preferred tools for assessing ICU-AW [14]. The most used voluntary methodology for evaluating ICU-AW is the 6-grade MRC sum score [2,15,41,42]. A score below 48 on the 6-grade MRC sum score indicates clinically evident muscle weakness. In contrast, a score below 36 suggests severe muscle weakness. However, it can be challenging to differentiate between higher scores [43]. Compared to the conventional 6-grade assessment, a modified 4-grade score demonstrated improved reliability in identifying ICU-AW. However, this approach still needs to undergo validation [44]. Hand-held dynamometry is commonly utilized to assess handgrip and quadriceps strength. However, concerns have been raised regarding its ability to provide a continuous quantitative measure [15,42,45]. Less commonly employed tools for assessing ICU-AW include the Scored Physical Function in Intensive Care Test, Functional Status Score for the ICU, and Chelsea critical care physical assessment tool. However, their use is less widespread [46]. The 6-MWD test is another assessment tool that measures patients' functional capacity and is utilized to evaluate their motor function [47]. Electrophysiological assessments are possible even when patients are unconscious and can distinguish between CIP and CIM. However, this approach is time-consuming, and expertise in this area may be limited.

Additionally, the significant co-occurrence of CIP and CIM can further complicate the differential diagnosis [41,48]. Direct muscle stimulation helps distinguish between CIP and CIM. Imaging techniques can measure muscle mass and quality, but the 4-compartment model is not practical in clinical settings. Clinicians must rely on accessible methods for assessing muscle mass and quality [49]. Numerous methods have been developed for identifying ICU-AW. However, in practical terms, the diagnosis relies primarily on clinical tests and electrophysiological studies after excluding underlying causes of neuromuscular disorders [29].

Dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), computed tomography (CT), and bioelectrical impedance analysis (BIA) are all methods to measure and quantify muscle size and quality [50]. MRIs and CTs are gold standards for evaluating muscle quality and quantity [50]. However, they are expensive, require extensive measurements, are not portable, and cannot assess larger individuals, along with radiation exposure [50]. DXA is a fast and simple method for measuring lean mass, which comprises both skeletal muscle mass and non-skeletal elements such as skin, connective tissue, and the fat-free portion of adipose tissue cells. However, DXA has some limitations, including high costs, exposure to radiation, limited equipment availability, and immobility of the patient [51,52]. BIA is an indirect method that uses electrical impedance to estimate muscle, lean, or fat-free mass. It involves running a low-level electrical current through the body and measuring the resistance, which is then used to calculate

the amount of muscle present in the body. However, several variables, including the instrument itself, the electrodes, the operator, the participant, and the surrounding environment, can affect the precision and reliability of the measurements. Therefore, BIA measurements must be interpreted cautiously and in conjunction with other assessment methods to obtain more accurate muscle mass estimation [52-54].

IMAGING

Computed Tomography

CT analysis offers precise body composition data divided into lean and fat tissue depots. Unlike other techniques that only measure overall lean body mass, CT can provide more detailed information [55]. Single-slice scans can predict whole-body muscular and fat mass in healthy and cancer-bearing populations. Still, this association needs to be better understood in ICU patients and can vary from image to image [55]. An important bone landmark is the third lumbar vertebra for measuring skeletal muscle mass [56]. Skeletal muscle boundaries are identified based on Hounsfield units (HUs) and specialized software, including ImageJ and Slice-O-Matic, can be utilized to determine the muscle cross-sectional area (CSA) [57]. CSA indicates how much the tissue attenuates the X-ray beam during the scan. Attenuation of muscle, a measure of muscle density, is associated with lipid deposition in skeletal muscle. It acts as a proxy for muscle quality [55,58]. Both CSA and muscle attenuation have a strong prognostic value, with lower values linked to poorer outcomes. Analysts' variability is generally less than 2% [59].

CT scans can provide valuable information on body composition but have limitations. One of the main drawbacks is the high radiation exposure during prospective CT scans. Consequently, CT can only be used to measure body composition if a CT scan has been performed for a medical condition [60]. Additionally, the thickness of slices and patient placement are crucial variables to consider. A patient's position during the scan and the relaxation state of muscles in the L3 region can influence the number of slices in the L3 and CSAs during the scan [60]. Another concern is that HUs can be altered by various factors, even though they primarily represent tissue attenuation. While some researchers have used average CT HUs to assess muscle quality, the validity of this method is still being determined and requires further research with muscle biopsies [61].

Dual-Energy X-Ray Absorptiometry

DXA is an advanced method for assessing body fat, lean muscle mass, and bone mineral mass that relies on X-ray attenuation principles like those used in CT but with considerably lower radiation exposure [62-65]. A DXA scan is preferred over a CT scan because of its safety and ease of access [66]. However, DXA scans only pass the energy beam down one side of the body, resulting in a planar image. DXA imaging uses two separate energy spectra—a "high" and a "low" energy level —to detect attenuation [67]. By calculating the R_{ST} in which R value represents the ratio of photon attenuation of soft tissue which is defined as the ratio of soft tissue attenuation at two photon energies (e.g., 40 keV and 70 keV), it can be predicted what the percentage of body mass is composed of the percentage of body fat (%fat) [67].

Common technological limitations in DXA include issues related to patient location, as well as differences between devices and software [68]. Physical limitations include the patient's height and weight, their level of hydration, and the timing of the scan about daily activities such as meal timing, bathroom habits, and exercise [69-71]. While slight variations in hydration are generally not thought to affect body composition measurements, disease-related fluid accumulation such as ascites or oedema can impact the results [70-72]. Additionally, this procedure is highly costly [49].

Bioimpedance

Bioimpedance is a technique for estimating body composition involving devices that fall into three categories: single-frequency, multiple-frequency, and spectroscopy. All these devices work by applying a low-intensity alternating electric current via surface electrodes at one or more radio frequencies. This current helps to determine the body's conductive and non-conductive tissue and fluid components [52,73]. The rate of the applied current varies based on the body's composition, including total body water, fat-free mass, or fat mass. Tissues rich in water and electrolytes, such as blood and muscle, conduct the current well, while tissues with more fat, bone, and air-filled spaces conduct the current poorly [49].

Bioimpedance involves measuring the body's resistance and reactance to a weak electrical current at different radio frequencies, which depends on the body's composition. Reactance refers to how the current interacts with membrane surfaces, while resistance generally refers to the current's ability to travel through fluid and tissues like cell membranes [73]. Equations based on impedance measurements estimate fluid and other

body composition compartments [52]. Bioimpedance measurements are useful for estimating metabolic activity and can be used therapeutically [74].

Bioimpedance, like DXA, is a reliable and convenient method for accumulating normative body composition data using single-frequency measurements. It can also measure nutrition-related markers beyond body composition, such as the 50-kHz phase angle, 200/5-kHz impedance ratio, and bioimpedance vector analysis [75]. Bioimpedance-generated estimates of body composition are subject to several assumptions that may not hold in a clinical setting, including fluid status, tissue hydration, and body geometry [76]. Obesity and fluid overload further complicate these methods' accuracy. Although BIS algorithms use different constants customized for each patient, they may still introduce errors. While improved algorithms can be applied in a research setting, applying them at the bedside presents significant challenges [49]. Currently, bioimpedance is the most convenient and precise tool for measuring body composition at the patient's bedside. However, notable variations between the different techniques need to be considered. Irrespective of the approach, standardized procedures are imperative when performing bioimpedance measurements. For investigations, it is recommended that only one technician use the same device and equation/algorithm [76].

Magnetic Resonance Imaging

MRI is a method for determining muscle CSA and volume that is non-invasive and free of radioactivity, and it provides excellent tissue differentiation capabilities. As a result, MRI is regarded as the standard for evaluating changes in muscle size. However, MRI imaging requires highly trained personnel and is limited by the cost of operations, availability and time-consuming post-acquisition processing [77].

Ultrasound

Clinical assessment is supplemented with volition and neurophysiology testing to diagnose ICU-AW. However, when patients receive mechanical ventilation, many are administered strong sedatives during the initial stages of critical illness. As a consequence, diagnosing ICU-AW may be delayed [78]. Ultrasound is a promising diagnostic tool for identifying individuals at risk of ICU-AW. It is a low-cost, non-invasive, widely available, and efficient imaging technique that can assess skeletal and respiratory muscles. The five main parameters used for ultrasound muscle assessment include muscle thickness, CSA, pennation angle, fascicle length, and echo intensity. Furthermore, researchers have identified four new potential parameters for ultrasound muscle assessment. These parameters include muscle volume, measuring muscle stiffness through elastography, evaluating the ability of a muscle to contract by comparing its CSA at rest and during maximal contraction, and assessing the microcirculation of a muscle [79].

Assessment of peripheral skeletal muscle

Research has shown that sarcopenia, which refers to the deterioration of muscle mass and strength with age, is more prominent in the lower limb muscles than in the upper limb muscles. Furthermore, there is a strong correlation between muscle strength and the CSA of the rectus femoris (RF) muscle. Studies conducted in ICU have shown that muscle mass can decrease rapidly, with a 10% decline in the RF' CSA within 7 days [80].

Assessment of respiratory muscles by ultrasound

Ultrasound technology has been used to assess respiratory muscles since Kai Haber et al., first utilized it to evaluate diaphragmatic motion in patients with intra-abdominal illnesses [81]. The diaphragm is the most significant respiratory muscle, accounting for almost 70% of total lung capacity [82]. Diaphragm excursion (DE) and diaphragm thickening fraction (TFdi) are the two most used ultrasonography markers for assessing diaphragm function. DE represents the distance the diaphragm extends from the end of expiration to the end of inspiration. TFdi represents the percentage by which the diaphragm thickens during inspiration. A healthy individual breathing deeply typically has a DE of 4.7–7.6 cm and a TFdi of 42%–78%. Although DE and TFdi are commonly considered indicators of extubation outcomes, their accuracy has been debated [83].

For successful extubation, compensatory action from the intercostal, sternocleidomastoid, abdominal muscles, and other accessory respiratory muscles is necessary when the diaphragm is not functioning properly. Thus, muscle ultrasonography to assess respiratory muscle weakness should include these additional muscles, particularly the parasternal intercostal muscles, which play an important role as supplementary inspiratory muscles. TFic, the thickening fraction of the parasternal intercostal muscle during inspiration, indicates respiratory muscle function when the diaphragm is ineffective [83].

The parasternal intercostal muscle's thickness at end-expiration is 3.3 mm in healthy males and 2.2 mm in healthy

females, with a typical TFic of 3% [84]. In Dres et al.'s study [84], which examined the relationship between TFic and respiratory stress, diaphragm function, and spontaneous breathing trial (SBT) outcomes, patients with lower levels of pressure support, diaphragm dysfunction, or SBT failure exhibited greater TFic than healthy individuals. Mechanically ventilated patients' TFic decreased with increasing pressure support, indicating a dose-response relationship between TFic and respiratory load. The predictive ability of TFdi >28.7% for extubation outcomes was comparable to that of TFic >9.5% in sensitivity and accuracy. While TFic and TFic/TFdi may not have significantly improved DE and TFdi as predictors of extubation outcomes, they provide healthcare providers with an alternative method and contribute to understanding the patient's balance between respiratory volume and capacity [83]. Evaluating the severity of respiratory problems can help determine when tracheostomies will be necessary and when mechanical ventilation will be weaned. If mechanical ventilation is prolonged or extubation fails, a tracheostomy may be required, while noninvasive mechanical ventilation and mechanically assisted coughing can help safely extubate patients with difficulty extubating [85]. Although ICU-AW complications are associated with higher mortality rates [86], longer ICU and hospital stays [87,88], and increased costs, it is often reversible within three weeks [89], though recovery may be incomplete [90,91], and prognosis may vary depending on the electrophysiological subtype, with CIP having a worse recovery prognosis compared to CIM [38,92]. The abdominal expiratory and lower limb muscles can also be evaluated by ultrasound to predict extubation outcomes in addition to the diaphragm and intercostals, especially for patients with suboptimal diaphragm or parasternal intercostal muscle function [93]. Muscle ultrasonography has yet to be extensively studied in diagnosing and predicting the prognosis of ICU-AW. Still, one study found that using ultrasound to measure the CSA of the RF and comparing it with frailty can effectively forecast the outcome of critically ill patients [94]. Another study observed that a larger CSA of the RF muscle on admission was associated with less muscle atrophy and fibre necrosis [95]. Additionally, the size of the quadriceps muscle as determined by ultrasound, has been linked with an increased risk of unplanned readmissions or mortality. Nevertheless, research has indicated that using ultrasound to measure muscle thickness (TH) for multiple muscles is not an accurate diagnostic tool [96]. According to a study in 2021 by Zhang et al. [39], changes in muscle ultrasound measurements using MRC criteria can effectively diagnose ICU-AW. The most effective cutoff ratios were a reduction of over 15% for muscle thickness (ΔTH day 10) and over 12% for CSA (ΔCSA day 10) in the lower extremity on the right side. As a result, muscle ultrasound can be considered a useful supplementary diagnostic tool for ICU-AW [39]. Although certain muscle parameter changes within 10 days effectively predict ICU-AW, SOFA and APACHE II scores during ICU admission are more advantageous in predicting ICU-AW occurrence. The latter scores are more time-efficient and easier to implement, with similar receiver operating characteristic-area under curve (ROC-AUC) scores compared to the changes in muscle parameters [97,98], even though muscle parameter changes over 10 days effectively predict ICU-AW, relying exclusively on them may not be necessary. At the same time, there are many validated predictors of ICU-AW; the SOFA and APACHE II scores can serve as indicators of multiple high-risk factors combined, making them more time-efficient and easier to implement. However, previous studies have shown that the SOFA and APACHE II scores alone are inadequate diagnostic tools [11,99]. Therefore, it is necessary to validate these findings further, considering the small sample size of the current study [39]. Table 1 shows the criteria for diagnosing ICU-AW from various imaging tests [100-107].

Preventive and Therapeutic Measures of ICU-AW

Unfortunately, there is still no cure for ICU-AW, while prevention has been successful when focusing on particular risk factors.

Avoiding Hyperglycemia

In two large trials, intensive insulin therapy with blood glucose levels below 110 mg/dl has been shown to reduce the risk of CIP and CIM, resulting in shorter periods of mechanical ventilation, shorter stays in the ICU, and a lower mortality rate over 180 days [20,108,109]. A study on Guillain-Barre syndrome also found blood glucose control to improve functional outcomes [6].

Avoiding Early Parenteral Nutrition

The optimal approach to nutritional management in the ICU, particularly in relation to early parenteral nutrition, is not fully comprehended. There is a recognized concern that using parenteral nutrition might have unfavorable consequences on ICU-AW risk, making enteral nutrition a more favorable choice [110]. Notably, it's intriguing to note that obesity offers some protection against ICU-AW risk. This safeguarding effect could

Table 1. Criteria for diagnosing ICU-AW from various imaging tests

Different types of imaging	Diagnostic criteria
Computed tomography	Through measured Fat volume: the total volume ratio to provide the overall fat percentage as a surrogate for muscle atrophy. Fat volume was defined as the summated volume of pixels with attenuation coefficients between −50 and −250 Hounsfield units, the known attenuation range for fat [100].
Dual-energy X-ray absorptiometry	Percent fat mass increased, whereas the lean mass decreased for the whole body, trunk, and legs [101].
Bioimpedance	Bioimpedance equation was developed for fat-free mass and may produce substantial scaling errors when compared against total body water measures. Studies that focus on evaluating a bioimpedance method's ability to measure changes in muscle volume or mass [102].
Magnetic resonance imaging	Extensive muscle atrophy, fatty infiltration (replacement of muscle with fat), and edema (fluid accumulation) within muscles show hyperintensity, which was more florid in the lower limbs and pelvic muscles. There is a lesser extent of involvement in the upper limbs, possibly due to a smaller volume of muscles in the upper extremity [103].
Ultrasound	• Decrease of muscle strength relates to muscle volume, the latter may be inferred from its CSA. Some authors tried to predict CSA directly from muscle thickness [104]. • Change in muscle composition can be gathered by quantification of muscle echogenicity [105]. • The angle of insertion of muscle fibers into the aponeurosis. This angle provides information about muscle strength, as the greater the pennation angle, the more the contractile material packed within a given volume and by inference, the higher is the muscle's capacity to generate force. The loss of pennation angle seemed to have high diagnostic accuracy for ICU-AW and could be assessed before patients became able to perform volitional tests, allowing for earlier diagnosis. Even if these results are considered as an exploratory background for more focused studies, the monitoring of changes to muscle architecture may lead to timely detection and better quantification of muscle loss [106,107].

ICU-AW: intensive care unit-acquired weakness; CSA: cross-sectional area.

likely be attributed to the presence of ketone bodies [111].

Amount of Calories

Even after adjusting for the severity of the illness, obtaining 80% of the recommended calories was related to lower mortality. However, significance needed to be recovered when accounting for the amount of proteins. This study shows that delivery of ≥80% of prescribed protein is associated with substantially reduced mortality, independently of energy intake. Furthermore, in the more severely injured or ill patients who stay in the ICU for 12 or more days, achieving ≥80% of prescribed protein also predicted a shorter time to discharge alive, an outcome that was independent of energy intake. The converse, that greater energy intake affected outcomes positively when adjusting for protein intake, could not be demonstrated. they could not see any beneficial association between greater energy intake and outcomes. Efforts to achieve >80% of the prescribed protein intake are warranted. However, further studies are needed to determine the optimal amount of protein that critically ill patients require to maximize their chances of survival and recovery [112]. Muscle atrophy and weakness have been linked to the caloric deficit caused by critical illness-related anorexia and gastrointestinal dysfunction [113].

Number of Proteins and Route of Nutrition

Early and complete enteral feeding is recommended to prevent muscle atrophy in critically ill patients, with parenteral supplementation as an option if necessary. Increasing protein supply in nutritional support is important to counter muscle protein depletion. Delaying the administration of parenteral nutrition beyond the first week may protect against ICU- AW, but the optimal timing for its introduction is uncertain [114-116].

Quality of Protein

It is advisable to consider the specific types of proteins or amino acids proven particularly advantageous in preserving muscle mass. A third or more of the proteins that make up muscle mass are branched-chain amino acids. Despite this, administering branched-chain amino acids has not improved the prognosis. The most extensively researched branched-chain amino acid is leucine. Research has linked its metabolites, alpha-isocaproate and beta-hydroxy-beta-methyl butyrate (HMB), to reduced protein catabolism under acute stress conditions and to ergogenic effects in muscle [117]. HMB has been demonstrated to minimize proteolysis and muscle damage, enhance lean mass and strength in young and older adults when accompanied by a physical exercise program [118-120],

and prevent muscle loss associated with bed confinement in healthy participants [121]. Obesity is found to have a protective effect on the risk of ICU-AW, which may be due to the presence of ketone bodies [111].

Minimizing Sedation and Early Mobilization

Early movement and physical therapy can lower the risk of ICU-AW. At the same time, daily sedative infusion stoppage can shorten mechanical ventilation and ICU stay, indirectly reducing the risk of ICU-AW [122]. High-frequency physiotherapy in the ICU has been suggested to improve quality of life at 6 months. Early rehabilitation has been found to strengthen only short-term physical-related outcomes. There is low-quality evidence for a reduced likelihood of ICU-AW compared to standard treatment or no early rehabilitation [123]. The current ICU approach emphasizes early mobilization through exercises, but more clinical trials are needed while considering patient pain. One-third of ICU-AW patients die in the acute phase, another third regain mobility within 4 months, and many experience long-term sensory loss, atrophy, or focal weakness [124].

Neuromuscular Electrical Stimulation

The use of Neuromuscular electrical stimulation (NMES) as a substitute for mobilization has been suggested. Despite a few small randomized controlled trials (RCTs) being carried out on critically ill patients with NMES of varying frequency, intensity, and duration, with some encouraging results, a recent systematic review and meta-analysis concluded that there was no significant difference between standard care and NMES in terms of muscular strength or reliance on mechanical ventilation and intensive care [125].

Drugs

(1) Anabolic hormones: although anabolic hormones such as growth hormone, insulin like growth factor -1, and nandrolone can increase muscle mass, they do not qualify as first-line therapy due to complications. Their use may be restricted to chronic critically ill patients [126]. (2) Beta-blockers: these are effective but only for oral use (propranolol). Inotropic medications which emphasize muscular dysfunction rather than atrophy by boosting intracellular calcium flux, beta-adrenergic agonists (fenoterol, not albuterol) have beneficial inotropic effects. Additionally, individuals with chronic bronchitis (chronic obstructive pulmonary disease) who had mechanical ventilation with the infusion of dopamine reported positive outcomes (diaphragmatic perfusion and cardiac output). Levosimendan, a calcium sensitizer, increases neuromechanical effectiveness and reduces contraction fatigue. These treatments were all identified in a systematic assessment of initially promising pharmaceutical approaches as unsuitable for routine use [127].

(3) Inflammatory modulation: treatment with intravenous immunoglobulins (IVIg) was linked to a lower incidence of ICU-AW, according to a retrospective review [128]. A RCT was conducted to determine whether early treatment with IgM-enriched IVIg could reduce ICU-AW in patients with multi-organ failure. Still, the problem was prematurely stopped due to the interventions [129]. (4) Cytokines are produced less when NF-kB is inhibited. On the other hand, although toll-like receptor 4's proteolytic effects are known, using a blocker of these receptors (eritoran) did not help septic patients' prognoses. New perspectives have been opened with the identification of novel inflammatory mediators such as GFD-15 [130].

(5) Contradictory effects of corticosteroids include the fact that. In contrast, low dosages of methylprednisolone (5 mg/kg) increase diaphragmatic dysfunction. In comparison, large doses of the drug (30 mg/kg) seem to shield the diaphragm from the negative effects of mechanical ventilation [131]. (6) Mesenchymal stem cell therapy has been shown to restore mitochondrial function in satellite cells in a mouse model of sepsis [132].

CONCLUSIONS

ICU-AW is a common and potentially life-threatening complication in ICU patients which can be prevented through reducing sedation, insulin therapy, and early mobilization. Although multiple methods have been developed for the detection of ICU-AW, each method has its own advantages and limitations. The bedside ultrasound has proven to be the most reliable, safe, and cost-effective tool for muscle assessment and detection of ICU-AW. The combination of the SOFA score, Acute Physiology and Chronic Health Evaluation (APACHE) II score assessment, and Ultrasound can be a convenient approach for the early detection of ICU-AW. This approach can facilitate timely intervention and prevent the catastrophic consequences associated with ICU-AW. However, further studies are necessary to reinforce the evidence supporting this approach.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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Conceptualization: HE, WA. Methodology: HE, WA. Formal analysis: HE, WA. Data curation: HE, WA. Visualization: HE, WA. Project administration: HE, WA. Writing–original draft: HE, WA. Writing–review & editing: all authors.

REFERENCES

1. Wang W, Xu C, Ma X, Zhang X, Xie P. Intensive care unit-acquired weakness: a review of recent progress with a look toward the future. Front Med (Lausanne) 2020;7:559789.
2. Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med 2009;37:S299-308.
3. Kramer CL. Intensive care unit-acquired weakness. Neurol Clin 2017;35:723-36.
4. Wilcox SR. Corticosteroids and neuromuscular blockers in development of critical illness neuromuscular abnormalities: a historical review. J Crit Care 2017;37:149-55.
5. Pattanshetty RB, Gaude GS. Critical illness myopathy and polyneuropathy: a challenge for physiotherapists in the intensive care units. Indian J Crit Care Med 2011;15:78-81.
6. Tortuyaux R, Davion JB, Jourdain M. Intensive care unit-acquired weakness: questions the clinician should ask. Rev Neurol (Paris) 2022;178:84-92.
7. Piva S, Fagoni N, Latronico N. Intensive care unit-acquired weakness: unanswered questions and targets for future research. F1000Res 2019;8:F1000 Faculty Rev-508.
8. Murthy S, Leligdowicz A, Adhikari NK. Intensive care unit capacity in low-income countries: a systematic review. PLoS One 2015;10:e0116949.
9. Farhan H, Moreno-Duarte I, Latronico N, Zafonte R, Eikermann M. Acquired muscle weakness in the surgical intensive care unit: nosology, epidemiology, diagnosis, and prevention. Anesthesiology 2016;124:207-34.
10. Li Z, Zhang Q, Zhang P, Sun R, Jiang H, Wan J, et al. Prevalence and risk factors for intensive care unit acquired weakness: a protocol for a systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e22013.
11. Wieske L, Witteveen E, Verhamme C, Dettling-Ihnenfeldt DS, van der Schaaf M, Schultz MJ, et al. Early prediction of intensive care unit-acquired weakness using easily available parameters: a prospective observational study. PLoS One 2014;9:e111259.
12. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874-82.
13. Rodriguez PO, Setten M, Maskin LP, Bonelli I, Vidomlansky SR, Attie S, et al. Muscle weakness in septic patients requiring mechanical ventilation: protective effect of transcutaneous neuromuscular electrical stimulation. J Crit Care 2012;27:319.
14. Wu Y, Zhang Z, Jiang B, Wang G, Wei H, Li B, et al. Current practice and barriers to ICU-acquired weakness assessment: a cross-sectional survey. Physiotherapy 2021;112:135-42.
15. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, et al. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med 2017;43:1270-81.
16. Yang T, Li Z, Jiang L, Wang Y, Xi X. Risk factors for intensive care unit-acquired weakness: a systematic review and meta-analysis. Acta Neurol Scand 2018;138:104-14.
17. Li M, Shao H, Wang C, Chen C, Ye L, Ding M, et al. Risk factors and their predictive value for intensive care unit acquired weakness in patients with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2021;33:648-53.
18. Eikermann M, Koch G, Gerwig M, Ochterbeck C, Beiderlinden M, Koeppen S, et al. Muscle force and fatigue in patients with sepsis and multiorgan failure. Intensive Care Med 2006;32:251-9.
19. Gordon BS, Kelleher AR, Kimball SR. Regulation of muscle protein synthesis and the effects of catabolic states. Int J Biochem Cell Biol 2013;45:2147-57.

20. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med 2007;175:480-9.
21. Brunello AG, Haenggi M, Wigger O, Porta F, Takala J, Jakob SM. Usefulness of a clinical diagnosis of ICU-acquired paresis to predict outcome in patients with SIRS and acute respiratory failure. Intensive Care Med 2010;36:66-74.
22. Derde S, Hermans G, Derese I, Güiza F, Hedström Y, Wouters PJ, et al. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med 2012;40:79-89.
23. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014;370:1626-35.
24. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev 2015;95:1025-109.
25. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Güiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab 2011;96:E633-45.
26. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013;1:621-9.
27. Latronico N, Friedrich O. Electrophysiological investigations of peripheral nerves and muscles: a method for looking at cell dysfunction in the critically ill patients. Crit Care 2019;23:33.
28. Ozdemir M, Bomkamp MP, Hyatt HW, Smuder AJ, Powers SK. Intensive care unit acquired weakness is associated with rapid changes to skeletal muscle proteostasis. Cells 2022;11:4005.
29. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med 2020;46:637-53.
30. De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med 2007;35:2007-15.
31. Jeong BH, Nam J, Ko MG, Chung CR, Suh GY, Jeon K. Impact of limb weakness on extubation failure after planned extubation in medical patients. Respirology 2018 Apr 11 [Epub]. https://doi.org/10.1111/resp.13305.
32. Zuercher P, Moret CS, Dziewas R, Schefold JC. Dysphagia in the intensive care unit: epidemiology, mechanisms, and clinical management. Crit Care 2019;23:103.
33. Hermans G, Van Aerde N, Meersseman P, Van Mechelen H, Debaveye Y, Wilmer A, et al. Five-year mortality and morbidity impact of prolonged versus brief ICU stay: a propensity score matched cohort study. Thorax 2019;74:1037-45.
34. Dres M, Dubé BP, Mayaux J, Delemazure J, Reuter D, Brochard L, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med 2017;195:57-66.
35. Medrinal C, Prieur G, Frenoy É, Robledo Quesada A, Poncet A, Bonnevie T, et al. Respiratory weakness after mechanical ventilation is associated with one-year mortality: a prospective study. Crit Care 2016;20:231.
36. Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, et al. Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. Crit Care Med 2017;45:446-53.
37. Wieske L, Dettling-Ihnenfeldt DS, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, et al. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Crit Care 2015;19:196.
38. Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatry 2008;79:838-41.
39. Zhang W, Wu J, Gu Q, Gu Y, Zhao Y, Ge X, et al. Changes in muscle ultrasound for the diagnosis of intensive care unit acquired weakness in critically ill patients. Sci Rep 2021;11:18280.
40. Amador T, Saturnino S, Veloso A, Ziviani N. Early identification of ICU patients at risk of complications: regularization based on robustness and stability of explanations. Artif Intell Med 2022;128:102283.
41. Kelmenson DA, Quan D, Moss M. What is the diagnostic accuracy of single nerve conduction studies and muscle ultrasound to identify critical illness polyneuromyopathy: a prospective cohort study. Crit Care 2018;22:342.
42. Vanpee G, Hermans G, Segers J, Gosselink R. Assessment of limb muscle strength in critically ill patients: a systematic review. Crit Care Med 2014;42:701-11.
43. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve 2012;45:18-25.
44. Parry SM, Berney S, Granger CL, Dunlop DL, Murphy L, El-Ansary D, et al. A new two-tier strength assessment approach to the diagnosis of weakness in intensive care: an observational study. Crit Care 2015;19:52.
45. Mehmet H, Yang AW, Robinson SR. Measurement of hand grip strength in the elderly: a scoping review with recommenda-

tions. J Bodyw Mov Ther 2020;24:235-43.
46. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care 2013;17:R156.
47. Salbach NM, O'Brien KK, Brooks D, Irvin E, Martino R, Takhar P, et al. Reference values for standardized tests of walking speed and distance: a systematic review. Gait Posture 2015;41:341-60.
48. Latronico N, Bertolini G, Guarneri B, Botteri M, Peli E, Andreoletti S, et al. Simplified electrophysiological evaluation of peripheral nerves in critically ill patients: the Italian multi-centre CRIMYNE study. Crit Care 2007;11:R11.
49. Teigen LM, Kuchnia AJ, Mourtzakis M, Earthman CP. The use of technology for estimating body composition: strengths and weaknesses of common modalities in a clinical setting. Nutr Clin Pract 2017;32:20-9.
50. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
51. Meza-Valderrama D, Marco E, Muñoz-Redondo E, Morgado-Pérez A, Sánchez MT, Curbelo Peña Y, et al. Musculoskeletal ultrasound shows muscle mass changes during post-acute care hospitalization in older men: a prospective cohort study. Int J Environ Res Public Health 2022;19:15150.
52. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis: part I. Review of principles and methods. Clin Nutr 2004;23:1226-43.
53. Beaudart C, Bruyère O, Geerinck A, Hajaoui M, Scafoglieri A, Perkisas S, et al. Equation models developed with bioelectric impedance analysis tools to assess muscle mass: a systematic review. Clin Nutr ESPEN 2020;35:47-62.
54. Gonzalez MC, Barbosa-Silva TG, Heymsfield SB. Bioelectrical impedance analysis in the assessment of sarcopenia. Curr Opin Clin Nutr Metab Care 2018;21:366-74.
55. Paris M, Mourtzakis M. Assessment of skeletal muscle mass in critically ill patients: considerations for the utility of computed tomography imaging and ultrasonography. Curr Opin Clin Nutr Metab Care 2016;19:125-30.
56. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985) 2004;97:2333-8.
57. Lambell KJ, Tierney AC, Wang JC, Nanjayya V, Forsyth A, Goh GS, et al. Comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the intensive care unit: a pilot cross-sectional study. JPEN J Parenter Enteral Nutr 2021;45:136-45.
58. Landrum LM, Java J, Mathews CA, Lanneau GS, Copeland LJ, Armstrong DK, et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: a Gynecologic Oncology Group study. Gynecol Oncol 2013;130:12-8.
59. Jones EJ, Bishop PA, Woods AK, Green JM. Cross-sectional area and muscular strength: a brief review. Sports Med 2008;38:987-94.
60. Bowden JC, Williams LJ, Simms A, Price A, Campbell S, Fallon MT, et al. Prediction of 90 day and overall survival after chemoradiotherapy for lung cancer: role of performance status and body composition. Clin Oncol (R Coll Radiol) 2017;29:576-84.
61. Kumar A, Moynagh MR, Multinu F, Cliby WA, McGree ME, Weaver AL, et al. Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. Gynecol Oncol 2016;142:311-6.
62. El Ghoch M, Pourhassan M, Milanese C, Müller MJ, Calugi S, Bazzani PV, et al. Changes in lean and skeletal muscle body mass in adult females with anorexia nervosa before and after weight restoration. Clin Nutr 2017;36:170-8.
63. Barbour LA, Hernandez TL, Reynolds RM, Reece MS, Chartier-Logan C, Anderson MK, et al. Striking differences in estimates of infant adiposity by new and old DXA software, PEAPOD and skin-folds at 2 weeks and 1 year of life. Pediatr Obes 2016;11:264-71.
64. Orgel E, Mueske NM, Sposto R, Gilsanz V, Freyer DR, Mittelman SD. Limitations of body mass index to assess body composition due to sarcopenic obesity during leukemia therapy. Leuk Lymphoma 2018;59:138-45.
65. Pelletier CA, Miyatani M, Giangregorio L, Craven BC. Sarcopenic obesity in adults with spinal cord injury: a cross-sectional study. Arch Phys Med Rehabil 2016;97:1931-7.
66. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33:997-1006.
67. Plank LD. Dual-energy X-ray absorptiometry and body composition. Curr Opin Clin Nutr Metab Care 2005;8:305-9.
68. Kerr A, Slater GJ, Byrne N, Nana A. Reliability of 2 different positioning protocols for dual-energy X-ray absorptiometry measurement of body composition in healthy adults. J Clin Densitom 2016;19:282-9.
69. Nana A, Slater GJ, Hopkins WG, Burke LM. Effects of daily activities on dual-energy X-ray absorptiometry measurements

of body composition in active people. Med Sci Sports Exerc 2012;44:180-9.
70. Norcross J, Van Loan MD. Validation of fan beam dual energy X ray absorptiometry for body composition assessment in adults aged 18-45 years. Br J Sports Med 2004;38:472-6.
71. Jayanama K, Putadechakun S, Srisuwarn P, Vallibhakara SA, Chattranukulchai Shantavasinkul P, Sritara C, et al. Evaluation of body composition in hemodialysis thai patients: comparison between two models of bioelectrical impedance analyzer and dual-energy X-ray absorptiometry. J Nutr Metab 2018;2018:4537623.
72. Shepherd JA, Ng BK, Sommer MJ, Heymsfield SB. Body composition by DXA. Bone 2017;104:101-5.
73. Matthie JR. Bioimpedance measurements of human body composition: critical analysis and outlook. Expert Rev Med Devices 2008;5:239-61.
74. Earthman C, Traughber D, Dobratz J, Howell W. Bioimpedance spectroscopy for clinical assessment of fluid distribution and body cell mass. Nutr Clin Pract 2007;22:389-405.
75. Ward LC. Bioelectrical impedance analysis for body composition assessment: reflections on accuracy, clinical utility, and standardisation. Eur J Clin Nutr 2019;73:194-9.
76. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. JPEN J Parenter Enteral Nutr 2015;39:787-822.
77. Erlandson MC, Lorbergs AL, Mathur S, Cheung AM. Muscle analysis using pQCT, DXA and MRI. Eur J Radiol 2016;85:1505-11.
78. Harvey PD. Clinical applications of neuropsychological assessment. Dialogues Clin Neurosci 2012;14:91-9.
79. Perkisas S, Bastijns S, Baudry S, Bauer J, Beaudart C, Beckwée D, et al. Application of ultrasound for muscle assessment in sarcopenia: 2020 SARCUS update. Eur Geriatr Med 2021;12:45-59.
80. van Ruijven IM, Stapel SN, Molinger J, Weijs PJ. Monitoring muscle mass using ultrasound: a key role in critical care. Curr Opin Crit Care 2021;27:354-60.
81. Boussuges A, Rives S, Finance J, Brégeon F. Assessment of diaphragmatic function by ultrasonography: current approach and perspectives. World J Clin Cases 2020;8:2408-24.
82. Fayssoil A, Behin A, Ogna A, Mompoint D, Amthor H, Clair B, et al. Diaphragm: pathophysiology and ultrasound imaging in neuromuscular disorders. J Neuromuscul Dis 2018;5:1-10.
83. Xue S, Xu M, Gu XP, Ma ZL, Liu Y, Zhang W. Advances in ultrasound assessment of respiratory muscle function. J Clin Anesth 2022;81:110914.
84. Dres M, Dubé BP, Goligher E, Vorona S, Demiri S, Morawiec E, et al. Usefulness of parasternal intercostal muscle ultrasound during weaning from mechanical ventilation. Anesthesiology 2020;132:1114-25.
85. Bernardes Neto SC, Torres-Castro R, Lima Í, Resqueti VR, Fregonezi GA. Weaning from mechanical ventilation in people with neuromuscular disease: a systematic review. BMJ Open 2021;11:e047449.
86. Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodóvar A, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med 2001;27:1288-96.
87. Wolfe KS, Patel BK, MacKenzie EL, Giovanni SP, Pohlman AS, Churpek MM, et al. Impact of vasoactive medications on ICU-acquired weakness in mechanically ventilated patients. Chest 2018;154:781-7.
88. Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. Crit Care Med 2005;33:349-54.
89. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859-67.
90. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348:683-93.
91. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011;364:1293-304.
92. Koch S, Wollersheim T, Bierbrauer J, Haas K, Mörgeli R, Deja M, et al. Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. Muscle Nerve 2014;50:431-6.
93. Formenti P, Umbrello M, Dres M, Chiumello D. Ultrasonographic assessment of parasternal intercostal muscles during mechanical ventilation. Ann Intensive Care 2020;10:120.
94. Mueller N, Murthy S, Tainter CR, Lee J, Riddell K, Fintelmann FJ, et al. Can sarcopenia quantified by ultrasound of the rectus femoris muscle predict adverse outcome of surgical intensive care unit patients as well as frailty? A prospective, observational cohort study. Ann Surg 2016;264:1116-24.
95. Puthucheary ZA, Phadke R, Rawal J, McPhail MJ, Sidhu

PS, Rowlerson A, et al. Qualitative ultrasound in acute critical illness muscle wasting. Crit Care Med 2015;43:1603-11.
96. Greening NJ, Harvey-Dunstan TC, Chaplin EJ, Vincent EE, Morgan MD, Singh SJ, et al. Bedside assessment of quadriceps muscle by ultrasound after admission for acute exacerbations of chronic respiratory disease. Am J Respir Crit Care Med 2015;192:810-6.
97. Horn J, Hermans G. Intensive care unit-acquired weakness. Handb Clin Neurol 2017;141:531-43.
98. de Jonghe B, Lacherade JC, Sharshar T, Outin H. Intensive care unit-acquired weakness: risk factors and prevention. Crit Care Med 2009;37:S309-15.
99. Witteveen E, Wieske L, Sommers J, Spijkstra JJ, de Waard MC, Endeman H, et al. Early prediction of intensive care unit-acquired weakness: a multicenter external validation study. J Intensive Care Med 2020;35:595-605.
100. Kubiak CA, Ranganathan K, Matusko N, Jacobson JA, Wang SC, Park PK, et al. Computed tomography evidence of psoas muscle atrophy without concomitant tendon wasting in early sepsis. J Surg Res 2019;234:210-6.
101. Chan KS, Mourtzakis M, Aronson Friedman L, Dinglas VD, Hough CL, Ely EW, et al. Evaluating muscle mass in survivors of acute respiratory distress syndrome: a 1-year multicenter longitudinal study. Crit Care Med 2018;46:1238-46.
102. Baldwin CE, Fetterplace K, Beach L, Kayambu G, Paratz J, Earthman C, et al. Early detection of muscle weakness and functional limitations in the critically ill: a retrospective evaluation of bioimpedance spectroscopy. JPEN J Parenter Enteral Nutr 2020;44:837-48.
103. Maramattom BV. Screening power of short tau inversion recovery muscle magnetic resonance imaging in critical illness myoneuropathy and guillain-barre syndrome in the intensive care unit. Indian J Crit Care Med 2022;26:204-9.
104. Dupont AC, Sauerbrei EE, Fenton PV, Shragge PC, Loeb GE, Richmond FJ. Real-time sonography to estimate muscle thickness: comparison with MRI and CT. J Clin Ultrasound 2001;29:230-6.
105. Pillen S, van Dijk JP, Weijers G, Raijmann W, de Korte CL, Zwarts MJ. Quantitative gray-scale analysis in skeletal muscle ultrasound: a comparison study of two ultrasound devices. Muscle Nerve 2009;39:781-6.
106. Strasser EM, Draskovits T, Praschak M, Quittan M, Graf A. Association between ultrasound measurements of muscle thickness, pennation angle, echogenicity and skeletal muscle strength in the elderly. Age (Dordr) 2013;35:2377-88.
107. Paolo F, Valentina G, Silvia C, Tommaso P, Elena C, Martin D, et al. The possible predictive value of muscle ultrasound in the diagnosis of ICUAW in long-term critically ill patients. J Crit Care 2022;71:154104.
108. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005;64:1348-53.
109. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev 2014;2014:CD006832.
110. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48-79.
111. Goossens C, Weckx R, Derde S, Dufour T, Vander Perre S, Pauwels L, et al. Adipose tissue protects against sepsis-induced muscle weakness in mice: from lipolysis to ketones. Crit Care 2019;23:236.
112. Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study. JPEN J Parenter Enteral Nutr 2016;40:45-51.
113. Gunst J, Van den Berghe G. Intensive care nutrition and post-intensive care recovery. Crit Care Clin 2018;34:573-83.
114. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr 2009;28:387-400.
115. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.
116. Walters J. Weakness in the intensive care unit. Pract Neurol 2022;22:358-75.
117. Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: a review. Nutr Metab (Lond) 2008;5:1.
118. Panton LB, Rathmacher JA, Baier S, Nissen S. Nutritional supplementation of the leucine metabolite beta-hydroxy-beta-methylbutyrate (hmb) during resistance training. Nutrition 2000;16:734-9.
119. Vukovich MD, Stubbs NB, Bohlken RM. Body composition in 70-year-old adults responds to dietary beta-hydroxy-beta-methylbutyrate similarly to that of young adults. J Nutr 2001;131:2049-52.
120. Gallagher PM, Carrithers JA, Godard MP, Schulze KE, Trappe SW. Beta-hydroxy-beta-methylbutyrate ingestion, Part I:

effects on strength and fat free mass. Med Sci Sports Exerc 2000;32:2109-15.
121. Deutz NE, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, et al. Effect of β-hydroxy-β-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. Clin Nutr 2013;32:704-12.
122. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7.
123. Fuke R, Hifumi T, Kondo Y, Hatakeyama J, Takei T, Yamakawa K, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. BMJ Open 2018;8:e019998.
124. Cameron S, Ball I, Cepinskas G, Choong K, Doherty TJ, Ellis CG, et al. Early mobilization in the critical care unit: a review of adult and pediatric literature. J Crit Care 2015;30:664-72.
125. Knutson JS, Makowski NS, Kilgore KL, Chae J. 43: Neuromuscular electrical stimulation applications. In: Webster JB, Murphy DP, editors. Atlas of orthoses and assistive devices. 5th ed. Elsevier; 2019. p. 432-9.e3.
126. Anderson LJ, Tamayose JM, Garcia JM. Use of growth hormone, IGF-I, and insulin for anabolic purpose: pharmacological basis, methods of detection, and adverse effects. Mol Cell Endocrinol 2018;464:65-74.
127. Shepherd SJ, Newman R, Brett SJ, Griffith DM; Enhancing Rehabilitation After Critical Illness Programme Study Investigators. Pharmacological therapy for the prevention and treatment of weakness after critical illness: a systematic review. Crit Care Med 2016;44:1198-205.
128. Werdan K. Pathophysiology of septic shock and multiple organ dysfunction syndrome and various therapeutic approaches with special emphasis on immunoglobulins. Ther Apher 2001;5:115-22.
129. Brunner R, Rinner W, Haberler C, Kitzberger R, Sycha T, Herkner H, et al. Early treatment with IgM-enriched intravenous immunoglobulin does not mitigate critical illness polyneuropathy and/or myopathy in patients with multiple organ failure and SIRS/sepsis: a prospective, randomized, placebo-controlled, double-blinded trial. Crit Care 2013;17:R213.
130. Su CM, Wang L, Yoo D. Activation of NF-κB and induction of proinflammatory cytokine expressions mediated by ORF7a protein of SARS-CoV-2. Sci Rep 2021;11:13464.
131. García-Martínez MÁ, Montejo González JC, García-de-Lorenzo Y Mateos A, Teijeira S. Muscle weakness: understanding the principles of myopathy and neuropathy in the critically ill patient and the management options. Clin Nutr 2020;39:1331-44.
132. Rocheteau P, Chatre L, Briand D, Mebarki M, Jouvion G, Bardon J, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun 2015;6:10145.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):425-434
https://doi.org/10.4266/acc.2023.00773

| pISSN 2586-6052 | eISSN 2586-6060

Healthcare-associated infections in critical COVID-19 patients in Tunis: epidemiology, risk factors, and outcomes

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Background: Coronavirus disease 2019 (COVID-19) pandemic disrupted adherences to healthcare-associated infection (HAI) prevention protocols. Herein, we studied the characteristics of all HAIs occurring in critically ill COVID-19 patients.

Methods: A retrospective, single-center cohort of critical COVID-19 patients during 2021. Microbiological samples were collected if HAI was suspected. We analyzed all factors that could potentially induce HAI, using septic shock and mortality as endpoints.

Results: Sixty-four among 161 included patients (39.7%) presented a total of 117 HAIs with an incidence density of 69.2 per 1,000 hospitalization days. Compared to the prior COVID-19 period (2013–2019), the identification of HAI increased in 2021. HAIs were classified into ventilator-associated pneumonia (VAP; n=38), bloodstream infection (n=32), urinary tract infection (n=24), catheter-related infection (n=12), and fungal infection (n=11). All HAIs occurred significantly earlier in the post–COVID-19 period (VAP: 6 vs. 10 days, P=0.045, in 2017 and 2021). *Acinetobacter baumannii* (39.5%) and *Klebsiella pneumoniae* (27%) were the most commonly isolated pathogens that exhibited a multidrug-resistant (MDR) profile, observed in 89% and 64.5%, respectively. The HAI factors were laboratory abnormalities (odds ratio [OR], 6.4; 95% confidence interval [CI], 2.3–26.0), cumulative steroid dose (OR, 1.9; 95% CI, 1.3–4.0), and invasive procedures (OR, 20.7; 95% CI, 5.3–64.0). HAI was an independent factor of mortality (OR, 8.5; P=0.004).

Conclusions: During the COVID-19 era, the incidence of HAIs increased and MDR isolates remained frequent. A severe biological inflammatory syndrome, invasive devices, and elevated cumulative steroid dosages were related to HAIs. HAI was a significant death factor.

Key Words: COVID-19; critical care; epidemiology; healthcare-associated infections; prognosis

Original Article

Received: June 2, 2023
Revised: September 25, 2023
Accepted: September 26, 2023

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by the novel corona virus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The COVID-19 pandemic disrupted healthcare systems around the world [1,2]. The large number of critically ill patients necessitated the rapid expansion of intensive care unit (ICU) bed capacity, which is commonly called as expanded ICU. In addition, there was a request from non-ICU units to strengthen human and logistical resources.

As a result, it was not easy to properly adhere to the guidelines for the prevention of health-

care-associated infections (HAIs). Several studies reported that the proportion of HAIs during the pandemic was higher compared to the period before the pandemic [3,4]. Indeed, patients with COVID-19 who required intensive care were more vulnerable to HAIs due to the use of invasive mechanical ventilation, co morbidities, immune suppression induced by both the SARS-CoV-2 infection and the severe disease itself, the use of immunomodulators (e.g., steroids) and other invasive life-sustaining procedures [5,6]. These factors inevitably had a detrimental impact on patient outcomes.

In this study, we sought to determine the incidence rates, the causative microorganisms with antimicrobial resistance profiles, the risk factors, and the impact of HAIs diagnosed in ICU patients hospitalized for critical COVID-19. Additionally, we compared the epidemiology of HAIs in the era of COVID-19 versus that before the onset of the pandemic.

KEY MESSAGES

- Compared to the pre-coronavirus disease 2019 era, ventilator-associated pneumonia, bloodstream infections, and urinary tract infections increased, while catheter-related infections decreased.
- The use of invasive devices, the presence of medical disorders, and higher cumulative steroid doses were independently related to healthcare-associated infections in COVID-19 patients.
- The risk of mortality among COVID-19 patients presenting HAIs increased by a factor of eight compared to those without any HAIs.

MATERIALS AND METHODS

Study Design and Ethical Status

This retrospective, single-center study was conducted in the medical ICU of a tertiary teaching hospital over a 9-month period (from January 2021 to September 2021). During this period, this facility experienced three significant peaks (January 2021, April 2021, and June/July 2021) of COVID-19 infections. Additionally, the ICU underwent logistical modifications to receive only critically ill COVID-19 patients.

The study was approved by the local Ethics Committee of La Rabta Hospital (No. 2021-I). Given the retrospective nature of this study, the need for written informed consent was waived.

Study Population

All eligible patients were 18yearsor older, were diagnosed with COVID-19 and required intensive care. SARS-CoV-2 infection was confirmed by a positive reverse transcription polymerase chain reaction test [7] from a nasopharyngeal swab. The patients who were discharged or who died within 48 hours of admission and those who had an infection that was not associated with healthcare were excluded from this study.

Main Endpoint

First, we determined the incidence rate of HAIs (at all locations combined and for each kind of HAI), described the microbiological characteristics, and compared the current epidemiology to that in the pre–COVID-19 era. Second, we studied the risk factors contributing to the occurrence of HAIs. Third, we assessed the impact of the HAI on the outcome parameters (namely septic shock, ventilator-free days, length of stay, and mortality). The comparison of the HAI epidemiology between the post–COVID-19 period versus the pre–COVID-19 period was performed based on the results of a study conducted in 2013 and published in 2017 [8] and to the unpublished local data of 2018 and 2019.

Microbiological Sampling Policy

In the presence of clinical or biological suspicion of HAI, the following microbiological cultures were prepared: a cytobacteriological examination of sputum was performed in patients with spontaneous breathing or via the tracheal aspiration (TA) of ventilated patients. For all patients with a suspected HAI, blood cultures were used to determine an aerobic or anaerobic environment, in addition to a cytobacteriological examination of urine (CBEU). Simultaneously, a fungal investigation was performed, including a blood culture on Sabouraud's medium and a colonization index on five sites (buccal, nasal, rectal, axillary, and inguinal).

Microbiologic Methods for Organism Identification

The Vitek 2 automated system (bioMérieux) was used for isolate identification and antimicrobial susceptibility testing. Minimum inhibitory concentrations were established according to the European Committee on Antimicrobial Susceptibility Testing breakpoints. For the identification of *Candida albicans*, the chlamydosporulation test on AT (Agar, Tween) or PCB (Potato, Carrot, Bile) medium was used. For *non-albicans* species, identification was based on the morphological appearance on AT or PCB media and on the Auxacolor sugar

assimilation gallery (Bio-Rad).

Definitions

Infections were considered health care associated if they occurred within a minimum of 48 hours following admission to the ICU. The following HAIs were diagnosed: ventilator-associated pneumonia (VAP), hospital-acquired pneumonia, urinary tract infection (UTI), bloodstream infection (BI), catheter-related infection (CRI), and suspected or proven invasive candidiasis. A documented bacterial infection was defined as the presence of a bacterium at a significant concentration (>10^6 in TA for VAP, >10^3 in the catheter culture for CRI, and >10^5 in the CBEU for UTI) and responsible for clinical or biological signs of sepsis.

Multidrug-resistant (MDR) bacteria were defined as all microorganisms resistant to at least one agent among three or more antimicrobial classes [9] and microorganisms known to have specific mechanisms of antibiotic resistance, such as *methicillin-resistant Staphylococcus aureus* (MRSA).

Collected Data

For each patient admitted for COVID-19, with an ICU-stay longer than 48 hours, the following information was collected and recorded in an electronic database: basic characteristics (age, sex, body mass index, ICU stay during the year prior to the current hospital admission, history of infection treated with antimicrobials during the year previous to admission, origin and length of stay before ICU admission, co morbidities, severity scores, biological data, use of invasive procedures, bacteriological and fungal results, and outcome data. Among the factors related to HAI, we studied the steroid cumulative dose that corresponded to dexamethasone at a dose of 6 mg/day for the entire duration of treatment.

To note that in the COVID-19, HAI+ group, outcome parameters of shock, pulmonary embolism, and other complications were considered when they occurred after HAI onset. This approach was used to avoid biasing the cause-and-effect link (HAI/complication) due to chronological factors.

Statistical Analyses

Descriptive quantitative variables were expressed as mean and standard deviation or median and interquartile range, according to the distribution. Categorical variables were reported as numbers and percentages. The groups (with HAI versus without HAI) were compared using parametric or non-parametric tests, according to the distribution of the data. The time scale of analysis was the period from the time of ICU admission until the date of discharge from the ICU or death. The HAI incidence rate was calculated as the number of HAI episodes per 1,000 days of ICU hospitalization for all included patients. The VAP incidence rate was calculated as the total number of VAP episodes during the study period divided by 1,000 days of ventilation for all patients included. The UTI incidence rate was calculated as the total number of UTI episodes during the study period divided by 1,000 days of bladder catheterization for all patients included. Comparisons of means (such as the time to onset of the different HAIs) were performed using the non-parametric Kruskal-Wallis test.

Risk factors for HAIs and those of mortality were both explored using logistic regression modeling. This multivariate analysis method involved factors with a P-value less than0.05 in the univariate analysis (COVID-19 patients with HAIs versus those without HAIs for the first analysis and between COVID-19 survivors vs. COVID-19 no survivors for the second). Each measure was expressed as an odds ratio (OR) with the corresponding 95% confidence interval (CI). All statistical tests were two-sided, and P<0.05 was selected to indicate statistical significance. Statistical analysis was performed using IBM SPSS ver. 20 software (IBM Corp.).

RESULTS

During the study period, 161 patients were included in the analysis. Among them, 64 (39.7%) presented 117 HAIs, resulting in an incidence density of 69.2 per 1,000 of hospitalization days, as illustrated in Figure 1.

Clinical Characteristics

The included patients had an average age of 58 years and were predominately male. The most frequently reported co morbidities were hypertension and diabetes. Nearly three-quarters of the patients had received antibiotics in the 3 months prior to admission, and 52% of the patients required invasive ventilation. Regarding steroids, for all infected patients, dexamethasone was administered at a dosage of 6 mg/day, but the duration of this regimen differed between patients. Thus, we present this result as a cumulative dose (mg per day). All clinical data (baseline and during follow-up) are provided in Table 1.

HAI Epidemiology

The most frequent HAI was due to VAP, accounting for 32.5%

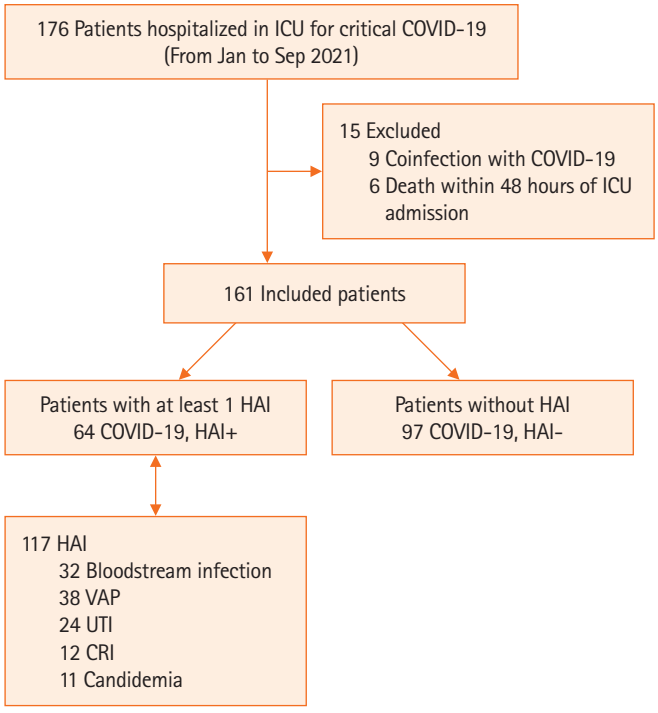


Figure 1. Study diagram. ICU: intensive care unit; COVID-19: coronavirus disease 2019; HAI: healthcare-associated infection; VAP: ventilator-associated pneumonia; UTI: urinary tract infection; CRI: catheter-related infection.

(n=38/117) of cases, occurring at a median time of 6 days after admission [3-9]. The second most frequent HAI was BI (n=32/117, 27.5%), which occurred at a median time of 7 days [4-12]. The predominant isolates in all HAIs were *Acinetobacter baumannii* and *Klebsiella pneumoniae* (39.5% and 27% of cases, respectively). *A. baumannii* had a profile of sensitivity to colistin in 89% of cases, and *K. pneumoniae* had an extended-spectrum beta-lactamase antibiotic-resistant profile in 64.5% of cases and carbapenem resistance in 26% of cases. Proportions of MDR among the other isolated species were *Pseudomonas aeruginosa* (45%), *Enterobacteriaceae* species other than *K. pneumoniae* (39%), *Staphylococcus aureus* (44%), and *Enterococci* (26%).

For fungal infections, 11 cases of candidemia were recorded, and *Candida albicans* was the exclusive isolate. A colonization index assessment was performed in 88 patients and was repeated two to three times (weekly) for 36 patients who stayed longer than 1 week. A total of 144 colonization indexes was obtained, of which 82 (57%) were positive, 48 were poorly colonized (colonization index <0.5), and 34 were ≥ 0.5. The most colonized sites were oral (n=60), anal (n=33), and nasal (n=29).

Table 1. Clinical characteristics

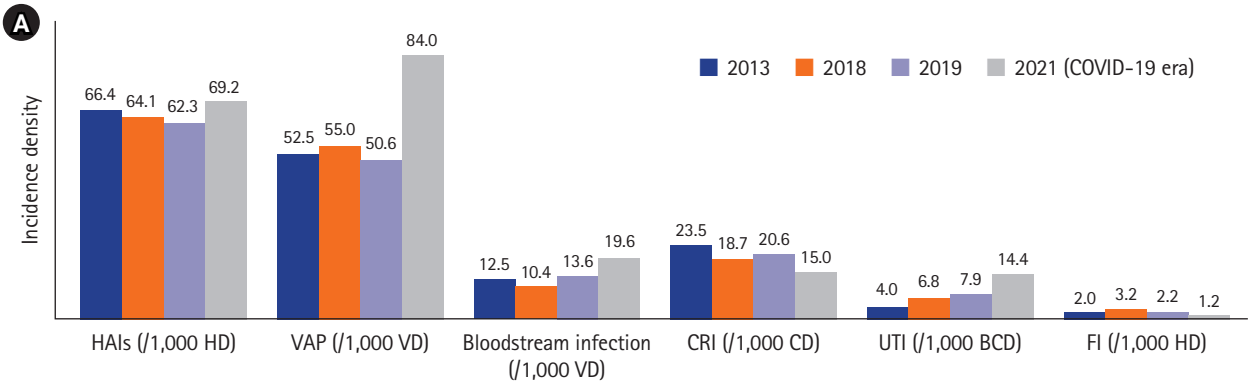
Variable	Value (n=161)
Age (yr)	58 (48–69)
Male: female	95:66
Origin	
Emergency room	95 (59)
LOS before ICU (day)	3 (2–5)
Comorbidity	
Hypertension	61 (38)
Diabetes mellitus	55 (34)
Cardiac failure	12 (7.5)
Dyslipidemia	33 (20.5)
Chronic respiratory failure	7 (4.5)
Chronic renal failure	15 (9.5)
Severity score	
SAPS II	30 (22–48)
APACHE II	16 (10–24)
SOFA	4 (3–4)
Hospitalization in a care structure the previous year	11 (7)
Antibiotics in the previous 3 months	117 (73)
CT scan lesions >50%	105 (65)
Invasive ventilation	84 (52)
Invasive device	
Venous catheter	88 (55)
Arterial catheter	46 (28.5)
Bladder catheterization	91 (57)
Antibiotic duration (day)	4 (2–8)
Steroid cumulative days (mg per day)	66 (48–90)
ECMO	2

Values are presented as median (interquartile range) or number (%).
LOS: length of stay; ICU: intensive care unit; SAPS: Simplified Acute Physiology Score; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; CT: computed tomography; ECMO: extracorporeal membrane oxygenation.

Candida albicans was most frequently isolated (54%), followed by *Candida glabrata* (23%).

Compared to the epidemiology before COVID-19 (in 2013, 2018, and 2019), there was an increase in the incidence density of HAIs, particularly regarding VAP and bacteremia. Conversely, the incidence of CRI decreased from 2013 to 2021 (Figure 2). The time to onset for all types of HAI was shorter in the COVID-19 period (Figure 2). The distribution of microorganisms involved in infections was similar between the two periods (before and during the COVID-19 era). However, during the COVID-19 period, we observed larger proportions of *A. baumannii* and *K. pneumoniae*, decreases of *P. Aeruginosa* and *Staphylococci*, and an increase of *Escherichia coli* (Figure 3).

A



B

Time to onset (day)	VAP	Bloodstream infection	CRI	UTI	FI
2013	10 (4–16)	12 (6–23)	16 (5–27)	13 (8–22)	32 (14–45)
2018	11 (4–15)	12 (6–23)	8 (3–18)	15 (9–27)	26 (10–38)
2019	10 (5–13)	12 (6–23)	11 (4–20)	12 (7–19)	19 (9–30)
2021 (COVID-19)	6 (3–9)	7 (4–12)	6 (4–8)	6 (4–9)	8 (6–14)
P-value	0.045	0.03	0.015	0.02	<0.001

Figure 2. Incidence density (A) and time to onset (B) of healthcare-associated infections (HAIs) before and during the coronavirus disease 2019 (COVID-19) era. 2013 results from [8]; 2018 and 2019 results: not published data. HD: hospitalization day; VAP: ventilator-associated pneumonia; VD: ventilator day; CRI: catheter-related infection; CD: catheter day; UTI: urinary tract infection; BCD: bladder catheterization day; FI: fungal infection.

HAI Risk Factors

Univariate analysis identified 13 variables as significant with P<0.05: age, hypertension, immunosuppression, hyperglycemia, elevated C-reactive protein (CRP), lymphopenia, reduced ratio of arterial blood (PaO_2) to fraction of inhaled oxygen (FiO_2) (P/F ratio), computed tomography (CT) lesions >50%, invasive ventilation, cumulative steroid dose, venous catheter, arterial catheter, and bladder catheterization (Table 2).

Given the limited number of patients (n=161) and the large number of variables to be included in the multivariate analysis (13 variables), we grouped certain variables into categories. The resulting six categories were as follows: age, comorbidities (hypertension and immunosuppression), laboratory abnormalities (hyperglycemia, elevated CRP, lymphopenia, reduced P/F), CT lesions > 50%, cumulative steroid dose, and invasive procedures (invasive ventilation, venous catheter, arterial catheter, and bladder catheterization). The factors associated with HAIs in COVID-19 patients in an ICU were biological abnormalities (OR, 6.4; 95% CI, 2.3–26.0), cumulative steroid dose > 60 mg per day (OR, 1.9; 95% CI, 1.3–4.0), and invasive procedures (OR, 20.7; 95% CI, 5.3–64.0).

Impact on Outcome

Patients who exhibited HAIs showed more frequent septic shock, greater numbers of ventilator days and ICU days, and higher mortality (Table 3). The analysis of mortality found that HAI was an independent factor of death in critical COVID-19 patients with an OR of 8.49 and a 95% CI of 2.56–32.00. Other poor prognosis cofactors were observed, including stage 3 acute respiratory distress syndrome, invasive ventilation, and septic shock, as shown in Table 4.

DISCUSSION

Compared to the pre-COVID-19 era, this study demonstrated a notable increase in HAIs in critical COVID-19 patients. Specifically, there were significant increases in VAP, UTIs, and BIs. Additionally, all types of HAIs had shorter onset during the COVID-19 period. *A. baumannii* and *K. pneumoniae* were the most commonly identified microorganisms. Invasive devices, biological disorders, and cumulative steroid dose were the independent factors of HAIs. COVID-19 patients presenting HAIs showed a higher incidence of septic shock and required greater ventilator days and ICU days. Mortality was significantly higher and HAI was an independent factor associated with

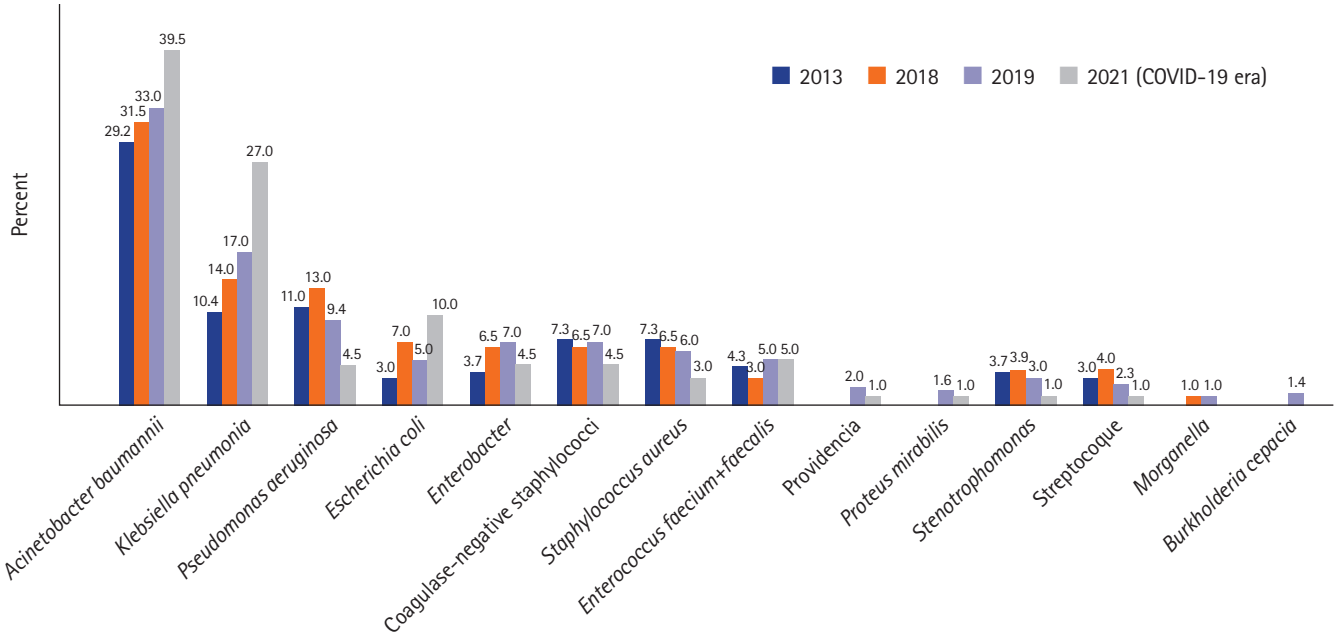


Figure 3. Distribution of microorganisms before and during corona virus disease 2019 (COVID-19) in percent (%). 2013 results from [8]; 2018 and 2019 results: not published data.

death (OR, 8.49; 95% CI, 2.56–32.00).

HAIs represent one of the most common adverse events in healthcare establishments [9-13]. At the onset of the COVID-19 pandemic, there was a reduction in HAIs, perhaps due to the strengthening of hygiene measures, mainly the use of hydroalcoholic gels [14].However, the massive influx of critical cases and the rapid reorganization of ICUs reduced the focus on traditional measures that reduce HAIs. We mentioned above that our unit underwent logistical and functional change during the pandemic. These changes briefly consisted of a rapid increase in ICU beds and the recruitment of caregivers from non-ICU services (all logistical and functional changes are presented in the Supplementary Material 1). We suggest that these changes might affect HAI models and contribute to the increase in HAI incidence. Moreover, the predominance of *Acinetobacter* and *Klebsiella* may represent an indirect witness to the failure of hygiene rules. In fact, their transmission essentially occurs via handling, inert surfaces, and invasive ventilation equipment. Furthermore, the higher density of patients likely contributed to an increase in the spread of these bacteria.

The increase in HAI incidence in COVID-19 patients has been previously described [15-17].The percentage of HAI among all patients in our series (39.7%) was similar to that of Somers et al. [17] in ventilated patients (40%). VAP occurred in 32.5% of our population, which was consistent with several previous results: 32.3% in a Chinese report [18] and 38% in a Spanish study [19]. A higher value was reported by an Italian study at 50% [20]. We explained the increase in VAP during COVID-19 by the respiratory tropism of the virus and the frequent use of ventilation, sedation, and neuromuscular blocking agents [21,22].

Our rate of BI (27.5%) was similar to that reported by Grasselli et al. (23.6%) [20] but was higher than that of a French study (14.9%) [23]. For UTIs, we showed an incidence of 22.2%. This was significantly higher than those reported by Grasselli et al. [20]: 7.7% [20], Falcone et al. [24]: 9.8%, and Bardi et al. [25]: 5%. Our incidence of CRI at 10.25% was close to that reported in the Italian study cited above (9.5%) [20], higher than that of Falcone et al. (6.6%)[24], and lower than that of Bardi et al.(20%) [25]. The changes and variability in the application of hygiene protocols may represent the main factor in explaining these gaps in incidences between countries. Nevertheless, these changes should be interpreted according to the COVID-19 situation (e.g., a surge in patients, medical supplement status), length of stay and exposure to invasive devices, the quality of programs for the prevention of HAIs, among other factors.

Unlike what we found for microorganisms, where Gram-negative bacilli predominated, the most commonly identified were *S. aureus*, both methicillin-susceptible and methicillin-resistant

Table 2. Comparison of all variables according to the occurrence of HAI (univariate analysis)

Variable	COVID-19, HAI+ (n=64)	COVID-19, HAI- (n=97)	P-value
Clinical variable			
Age (yr)	60 (52–71)	55 (44–63)	0.02
Male:female	36:28	59:38	0.62
ER origin	38 (60)	57 (59)	1.00
Stay before ICU (day)	3 (1–5)	3 (2–6)	0.06
Comorbidity			
Hypertension	34 (53)	27 (28)	0.002
Diabetes	27 (42)	28 (29)	0.09
Heart failure	6 (9)	6 (6)	0.54
Dyslipidemia	11 (17)	22 (23)	0.43
Chronic respiratory failure	5 (8)	3 (3)	0.15
Chronic renal failure	8 (13)	7 (7)	0.27
Immunosuppression	6 (9)	2 (2)	0.05
SOFA score	4 (3–4)	4 (3–4)	0.18
Antimicrobials in the previous 3 months	43 (67)	74 (76)	0.21
Laboratory and CT variable			
Hyperglycemia on admission	48 (75)	36 (37)	<0.001
D-dimers (μg/L)	1,305 (677–2,640)	1,086 (651–1,777)	0.19
CRP (mg/L)	134 (75–238)	104 (48–170)	0.02
WBC (x10^3/ml)	9.2 (6.6–13.9)	8.4 (6.4–11.8)	0.12
Lymphocytes (cells/ml)	590 (442–860)	750 (540–1,090)	0.01
P/F ratio	75.5 (63–91)	92 (67–131)	0.02
CT scan lesions >50%	51 (80)	54 (56)	0.01
Therapeutic variable			
Invasive ventilation	56 (88)	28 (29)	<0.001
Antimicrobial duration (day)	4 (3–7)	4 (2–6)	0.70
Steroid cumulative dose (mg/day)	72 (54–102)	60 (42–72)	0.001
ECMO	1	1	1.00
Venous catheter	58 (90)	30 (31)	<0.001
Femoral	57	31	<0.001
Under keyboard	4	1	0.08
Chinstrap	17	3	<0.001
Arterial catheter	36 (56)	10 (11)	<0.001
Femoral	4	1	0.07
Radial	33	8	<0.001
Bladder catheterization	61 (96)	30 (31)	<0.001

Values are presented as median (interquartile range) or number (%).
HAI: healthcare-associated infection; COVID-19: corona virus disease 2019; ER: emergency room; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; CT: computed tomography; CRP: C-reactive protein; WBC: white blood cell; P/F ratio: ratio of arterial blood (PaO_2) to fraction of inhaled oxygen (FiO_2); ECMO: extracorporeal membrane oxygenation.

Table 3. Impact of HAIs on outcome

Outcome parameter	COVID-19, HAI+ (n=64)	COVID-19, HAI- (n=97)	P-value
Shock	45 (70.0)	18 (18.5)	<0.001
Septic	41 (64.0)	13 (13.4)	<0.001
Cardiogenic	1 (1.5)	5	0.020
Mixed	3 (4.6)	0	-
Pulmonary embolism	7 (11.0)	4 (4.0)	0.110
Other complication	4 (6.3)	2 (2.0)	0.009
Myocarditis	0	1	-
Arrhythmia	2	0	-
Coronary insufficiency	1	1	-
Vein thrombosis	1	0	-
Ventilator day	6 (3–0)	2 (1–4)	<0.001
ICU LOS	12 (5–19)	8 (3–13)	0.002
Mortality	54 (84.3)	33 (34.0)	<0.001

Values are presented as number (%) or median (interquartile range).
HAI: healthcare-associated infection; COVID-19: corona virus disease 2019; ICU: intensive care unit; LOS: length of stay.

S. aureus followed by *Pseudomonas* in other reports [16,17,26]. Invasive procedures were strongly associated with HAIs. In fact, a patient is often infected by their own germs during invasive care (surgical procedures, invasive ventilation, vascular catheterization, urinary catheterization, etc.), and caregivers act as a vector of transmission. Otherwise, the association between CRP and HAI was observed by Falcone et al. [24], where a CRP on admission >7 mg/dl increased the risk of HAI with an OR of 3.59 and a 95% CI of 1.7–7.7 (P=0.001). High white blood cell and procalcitonin levels were associated with HAI with respective OR of 8.38 (95% CI, 1.07–65.55; P=0.04) and 4.92 (95% CI, 1.39–17.33; P=0.013) [27]. Hyperglycemia may be a consequence of a systemic inflammatory response and may serve as a marker of immunocompetence [28,29]. Consistent with our result, some reports found that hyperglycemia represents a risk factor for HAI [28,29].

The other factor we identified as influential was steroids. The latter exerts an inhibitory effect on the acquired and innate immune system. Therefore, this increases the risk of infection depending on the dose and time. Steroids should be used in a targeted manner, particularly in the context of infectious pathologies. Several studies reported that mortality increased when HAI occurred in critically ill patients [16,18,19,25,30]. Patients with HAI had longer ventilation days (OR, 3.31; 95% CI, 1.67–6.56; P=0.001), longer ICU stays (OR, 1.90; 95% CI, 1.06–3.40; P=0.03), and a higher 60-day mortality (OR, 1.86; 95% CI, 1.05–3.29; P=0.03) in a large multicenter study [16]. Mortality

Table 4. Factors related to mortality

Variable	Survivor (n=74)	Non survivor (n=87)	P-value	Multivariable analysis, OR (95% CI)
HAI	10 (13.5)	54 (62.0)	<0.001	8.5 (2.6–32.0) (P=0.004)
Male:female (ratio)	46:28 (1.64)	49:38 (1.28)	0.520	-
Age (yr)	56 (49–67)	61 (53–71)	0.006	NS
SOFA score	3.5 (2–4)	4.0 (3–4)	0.040	NS
P/F ratio	96 (75–135)	73 (61–90)	<0.001	NS
Stage 3 ARDS	33 (44.6)	72 (83.0)	<0.001	7.2 (2.1–26.6) (P=0.007)
Invasive ventilation	5 (6.7)	79 (91.0)	<0.001	23.5 (9.9–84.0) (P<0.001)
Septic shock	5 (6.7)	49 (56.5)	<0.001	9.8 (4.0–38.7) (P=0.002)

Values are presented as number (%)or median (interquartile range).
OR: odds ratio; CI: confidence interval; HAI: healthcare-associated infection; SOFA: Sequential Organ Failure Assessment; P/F ratio: ratio of arterial blood (PaO_2) to fraction of inhaled oxygen (FiO_2); ARDS: acute respiratory distress syndrome.

was twice as likely when HAI was complicated by septic shock, whereas uncomplicated infections did not affect mortality [20]. Septic shock was also a factor of mortality in our series (OR, 9.8; 95% CI, 4.0–38.7).

Our study reports original results focused on the particular context of the COVID-19 outbreak. This work enriches our national registry on HAIs. The comparison with previous epidemiology adds a point of strength. However, this work has certain limitations: first, the retrospective and single-center design could influence the validity of our conclusions. Second, the small sample size could affect the multivariate analysis because we grouped several variables into categories to compensate for the small sample size. Third, the lack of cost estimates regarding HAIs may be considered a limitation.

We concluded that the rate of HAIs increased from the pre–COVID-19 period to the COVID-19 pandemic period and this was mostly related to increased VAP and UTI complications. MDR isolates continued to be the pathogens most frequently responsible for these infections. The most highly related factors were severe biological inflammatory syndrome, invasive devices, and elevated cumulative steroid dose. We found that an HAI amplified the risk of death by a factor of eight. These findings indicate the need to develop a continuous surveillance system to identify and fight HAIs and strengthen procedures in the event of a pandemic.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

The abstract of this paper was presented as Flash-Com (FC 135, title: Healthcare-Related Infections in Critical Patients with COVID-19: Epidemiology, Risk Factors and Outcomes) at the Congress of the French Intensive Care Society (FICS) on June 23, 2022, in Paris (Palais de Congrès de Paris, Porte Maillot), France.

All the authors express their gratitude to Mr. Moez Ghrairi, English faculty member, for his help in proofreading this research paper.

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AUTHOR CONTRIBUTIONS

Conceptualization: AT. Methodology: AT. Formal analysis: BT. Data curation: SS, LM, ES. Visualization: SS, AM, LM, ES, BT. Writing–original draft: AT. Writing–review & editing: SA.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.00773.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Conway Morris A, Kohler K, De Corte T, Ercole A, De Grooth HJ, Elbers PW, et al. Co-infection and ICU-acquired infection in COIVD-19 ICU patients: a secondary analysis of the UNITE-COVID data set. Crit Care 2022;26:236.
3. Despotovic A, Milosevic B, Milosevic I, Mitrovic N, Cirkovic A, Jovanovic S, et al. Hospital-acquired infections in the adult intensive care unit-Epidemiology, antimicrobial resistance patterns, and risk factors for acquisition and mortality. Am J Infect Control 2020;48:1211-5.
4. Barrasa H, Martín A, Maynar J, Rello J, Fernández-Torres M, Aguirre-Quiñonero A, et al. High rate of infections during ICU admission of patients with severe SARS-CoV-2 pneumonia: a matter of time? J Infect 2021;82:186-230.
5. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 2020;81:266-75.
6. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care 2020;10:119.
7. Hanson KE, Caliendo AM, Arias CA, Englund JA, Hayden MK, Lee MJ, et al. Infectious Diseases Society of America Guidelines on the Diagnosis of Coronavirus Disease 2019 (COVID-19): serologic testing. Clin Infect Dis 2020;ciaa1343.
8. Trifi A, Abdellatif S, Oueslati M, Zribi M, Daly F, Nasri R, et al. Nosocomial infections: current situation in a resuscitation-unit. Tunis Med 2017;95:179-84.
9. Schwendimann R, Blatter C, Dhaini S, Simon M, Ausserhofer D. The occurrence, types, consequences and preventability of in-hospital adverse events: a scoping review. BMC Health Serv Res 2018;18:521.
10. World Health Organization. Patient safety fact file [Internet]. World Health Organization; 2019 [cited 2023 Sep 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/patient-safety
11. Haque M, Sartelli M, McKimm J, Abu Bakar M. Health care-associated infections: an overview. Infect Drug Resist 2018;11:2321-33.
12. Peters A, Tartari E, Mai SH, Allegranzi B, Pittet D. 2019 WHO hand hygiene campaign and global survey: clean care for all-it's in your hands. Lancet Infect Dis 2019;19:463-4.
13. Saito H, Allegranzi B, Pittet D. 2018 WHO hand hygiene campaign: preventing sepsis in health care and the path to universal health coverage. Lancet Infect Dis 2018;18:490-2.
14. Roshan R, Feroz AS, Rafique Z, Virani N. Rigorous hand hygiene practices among health care workers reduce hospital-associated infections during the COVID-19 pandemic. J Prim Care Community Health 2020;11:2150132720943331.
15. Baccolini V, Migliara G, Isonne C, Dorelli B, Barone LC, Giannini D, et al. The impact of the COVID-19 pandemic on healthcare-associated infections in intensive care unit patients: a retrospective cohort study. Antimicrob Resist Infect Control 2021;10:87.
16. Petty LA, Flanders SA, Vaughn VM, Ratz D, O'Malley M, Malani AN, et al. Risk factors and outcomes associated with community-onset and hospital-acquired coinfection in patients hospitalized for coronavirus disease 2019 (COVID-19): a multihospital cohort study. Infect Control Hosp Epidemiol 2022;43:1184-93.
17. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis 2021;73:e445-54.
18. He Y, Li W, Wang Z, Chen H, Tian L, Liu D. Nosocomial infection among patients with COVID-19: a retrospective data analysis of 918 cases from a single center in Wuhan, China. Infect Control Hosp Epidemiol 2020;41:982-3.
19. Soriano MC, Vaquero C, Ortiz-Fernández A, Caballero A, Blandino-Ortiz A, de Pablo R. Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19. J Infect 2021;82:e20-1.
20. Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, et al. Hospital-acquired infections in critically ill patients with COVID-19. Chest 2021;160:454-65.
21. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782-93.
22. Luyt CE, Bouadma L, Morris AC, Dhanani JA, Kollef M, Lipman J, et al. Pulmonary infections complicating ARDS. Intensive Care Med 2020;46:2168-83.
23. Kokkoris S, Papachatzakis I, Gavrielatou E, Ntaidou T, Ischaki E, Malachias S, et al. ICU-acquired bloodstream infections in critically ill patients with COVID-19. J Hosp Infect 2021;107:95-7.
24. Falcone M, Tiseo G, Giordano C, Leonildi A, Menichini M, Vecchione A, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. J AntimicrobChemother 2021;76:1078-84.
25. Bardi T, Pintado V, Gomez-Rojo M, Escudero-Sanchez R, Azzam

Lopez A, Diez-Remesal Y, et al. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis 2021;40:495-502.
26. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2021;27:83-8.
27. Cheng K, He M, Shu Q, Wu M, Chen C, Xue Y. Analysis of the risk factors for nosocomial bacterial infection in patients with COVID-19 in a tertiary hospital. Risk Manag Healthc Policy 2020;13:2593-9.
28. Kyi M, Colman PG, Wraight PR, Reid J, Gorelik A, Galligan A, et al. Early intervention for diabetes in medical and surgical inpatients decreases hyperglycemia and hospital-acquired infections: a cluster randomized trial. Diabetes Care 2019;42:832-40.
29. Khaodhiar L, McCowen K, Bistrian B. Perioperative hyperglycemia, infection or risk? Curr Opin Clin Nutr Metab Care 1999;2:79-82.
30. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):435-441
https://doi.org/10.4266/acc.2023.00451

| pISSN 2586-6052 | eISSN 2586-6060

Combining reservoir mask oxygenation with high-flow nasal cannula in the treatment of hypoxemic respiratory failure among patients with COVID-19 pneumonia: a retrospective cohort study

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Background: Concerns regarding positive-pressure-ventilation for the treatment of coronavirus disease 2019 (COVID-19) hypoxemia led the search for alternative oxygenation techniques. This study aimed to assess one such method, dual oxygenation, i.e., the addition of a reservoir mask (RM) on top of a high-flow nasal cannula (HFNC).

Methods: In this retrospective cohort study, the records of all patients hospitalized with COVID-19 during 2020–2022 were reviewed. Patients over the age of 18 years with hypoxemia necessitating HFNC were included. Exclusion criteria were positive-pressure-ventilation for any indication other than hypoxemic respiratory failure, transfer to another facility while still on HFNC and "do-not-intubate/resuscitate" orders. The primary outcome was mortality within 30 days from the first application of HFNC. Secondary outcomes were intubation and admission to the intensive care unit.

Results: Of 659 patients included in the final analysis, 316 were treated with dual oxygenation and 343 with HFNC alone. Propensity for treatment was estimated based on background diagnoses, laboratories and vital signs upon admission, gender and glucocorticoid dose. Inverse probability of treatment weighted regression including age, body mass index, Sequential Organ Failure Assessment (SOFA) score and respiratory rate oxygenation index showed treatment with dual oxygenation to be associated with lower 30-day mortality (adjusted hazard ratio, 0.615; 95% confidence interval, 0.469–0.809). Differences in the secondary outcomes did not reach statistical significance.

Conclusions: Our study suggests that the addition of RM on top of HFNC may be associated with decreased mortality in patients with severe COVID-19 hypoxemia.

Key Words: COVID-19; hypoxia; pneumonia

Original Article

Received: February 26, 2023
Revised: May 18, 2023
Accepted: August 1, 2023

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INTRODUCTION

Hypoxemic respiratory failure is the most feared complication of novel coronavirus (coronavirus disease 2019 [COVID-19]) pneumonia [1]. Affecting more than 14% of patients hospitalized with COVID-19, this is the leading cause of both intensive care unit (ICU) admissions and mortality in this population [2]. Positive pressure ventilation—both invasive and nonin-

vasive—has been long accepted as the most effective method of improving oxygenation [3]. Nonetheless, various concerns regarding the availability of these treatments (including shortages in ventilators and skilled operators), have lead the quest for alternative methods of oxygenation [4], aimed at alleviating the burden of invasive and noninvasive positive pressure ventilation and theirs potential complications.

One such method, often denominated as "dual oxygenation" and vastly implemented in our tertiary care medical center, is the addition of a reservoir mask (RM) on top of a high-flow nasal cannula (HFNC). HFNC has been extensively shown to improve oxygenation by reducing effective dead space ventilation and markedly increasing the fraction of inspired oxygen (FiO_2) [5], as well as significantly increasing the end expiratory pressure [6]. This modality was also shown to reduce 30-day mortality compared to other noninvasive measures [7]. Some alterations to the flow rate and oxygen concentrations of HFNC [8], the effect of manipulating the delivery device [9], opening to shutting the patient's mouth [6] or the addition of a surgical mask on top of the HFNC have been empirically evaluated [10]. This study aimed to evaluate the effects of dual oxygenation, i.e., the addition of RM on top of HFNC aiming to increase the amount of oxygen delivered to the alveoli in the attempt to avoid the need for invasive ventilation, compared to HFNC alone, on clinically significant outcome measures in the treatment of COVID-19 associated hypoxemic respiratory failure.

KEY MESSAGES

- We investigated a simple, readily available, safe, and yet not sufficiently researched oxygenation method: the addition of a reservoir mask on top of high flow oxygen cannula.
- Our data suggest this rudimentary intervention can be associated with decreased 30-day mortality.
- These findings could be extremely important for clinicians and incentivize further studies.

MATERIALS AND METHODS

This human study was approved by the Institutional Ethics Committee of Rambam Medical Center (No. 0228-21-RMC-D). The requirement for consent was waived by the ethics committee due to the retrospective nature of this study.

This retrospective cohort study aimed to compare the treatment of severely hypoxemic COVID-19 patients with either HFNC alone (control) or dual oxygenation (HFNC with the addition of a RM). The study was conducted in Rambam Healthcare Campus, a tertiary level care 1,100 beds medical center, situated in Haifa, Israel. The Electronic Health Registry files of all patients hospitalized between January 1, 2020, and December 31, 2022, in any one of eight dedicated COVID-19 wards were reviewed. To be included, a patient had to have had (1) a positive polymerase chain reaction test for COVID-19 performed within 2 days of hospital admission, (2) severe hypoxemia requiring the use of HFNC, defined as pulse oxygen saturation (SpO_2) persistently below 90% despite maximal flow (15 L/min) on RM, and (3) 18 years of age or older. Exclusion criteria were (1) positive pressure ventilation (either noninvasive or invasive) initiated for any reason other than refractory hypoxemia (e.g., general anesthesia), (2) transfer to another facility while still on HFNC, and (3) patients with do-not-resuscitate (DNR) or do-not-intubate (DNI) orders at any point during the hospitalization.

All patients were continuously monitored by pulse-oximetry. For HFNC, a flow of 40 L/min heated to 37 °C and humidified to 100% was used, at FiO_2 of 40%–100%, titrated to achieve capillary SpO_2 of 90%–95%. RM was added via a non-rebreather mask at a fixed oxygen flow of 15 L/min at ambient temperature. Invasive mechanical intubation was performed at the attending physician's discretion, mostly because of decreasing SpO_2 despite maximal non-invasive respiratory support. The primary outcome was mortality within 30 days from the first application of HFNC. Secondary outcomes were the initiation of invasive intermittent positive pressure ventilation (i.e., intubation) and admission to an ICU.

Statistical Analysis

Standard descriptive statistics were used to summarize population characteristics. Survival analysis was performed using the Gehan-Breslow-Wilcoxon method and visualized by means of a Kaplan-Meier survival plot. Cox regression was performed for multivariate survival analysis. Propensity for the treatment group was calculated by logistic regression, based on a priori selected variables. Inverse probability of treatment weighting was selected due to the similar sample sizes of the intervention (dual) and control (HFNC alone) groups. A two-sided $P < 0.05$ was considered statistically significant for all tests. Assuming patients treated with dual oxygenation to comprise at least 40% of the analyzed population the minimal total

sample size needed to detect a relative hazard of 0.8 or lower (with β=0.2) for the primary outcome of 30 days mortality was calculated to be 657. Statistical analysis was performed using IBM SPSS software ver. 24.0 (IBM Corp.).

RESULTS

Of 5,324 patients hospitalized with COVID-19 during the study period, 721 (13.5%) were treated with HFNC. Nine patients (1.2%) were excluded for being intubated for surgery, 17 (2.4%) were transferred to another facility while still requiring high-flow oxygenation, and 36 (5%) had DNR or DNI orders. A total of 659 patients were included in the final analysis: 343 (52%) were treated with HFNC alone (controls) and 316 patients (48%) were treated with dual oxygenation (the combination of HFNC and RM), as summarised in Figure 1. The characteristics of both groups are presented in Table 1.

The background diagnoses of solid and hematological malignancies, heart failure and dyslipidemia were significantly (P<0.05) more prevalent in the dual oxygenation group. Patients treated with dual oxygenation had higher mean white blood cells count (5.6±12.9 vs. 3.8±7.4 $\times 10^3/\mu l$, P=0.019), blood lactate (0.7±1.0 vs. 1.0±1.1 mMol/L, P<0.001) and C-reactive protein levels (6.6±9.9 vs. 9.1±10.7 mg/dl, P=0.002). The respiratory rate oxygenation (ROX) index measured at 6 hours after the initial application of HFNC was significantly higher in the dual oxygenation group (4.7±1.4 vs. 4.4±1.1, P=0.003). There were no significant differences between the two groups in the lowest Sequential Organ Failure Assessment (SOFA) score during hospitalization, as well as length of treatment or total dose of corticosteroids administered. Rates of, time to and duration of noninvasive bilevel positive airway pressure support, days spent using HFNC, and body mass indexes were similar in both groups.

At 30 days from the initial application of HFNC, the primary outcome of all-cause mortality was significantly lower in the dual oxygenation group (104 [32.9%] vs. 146 [42.6%], P=0.011). The lower proportion of invasive positive pressure ventilation in the dual oxygenation group within 30 days from HFNC initiation (46 [14.6%] vs. 65 [19%], P=0.132) did not reach statistical significance. Rates of ICU admission within 30 days from HFNC initiation were similar between groups (93 [29.3%] and 100 [29.2%], P=0.938). Survival analysis of both primary and secondary outcomes are visualized Figure 2.

Assessing for potential confounders, propensity for the treatment group (dual vs. control) was scored using a set of antecedently selected independent variables. These included gender, background diagnoses (solid and hematological malignancy, hypertension, heart failure, ischemic heart disease, atrial fibrillation, dyslipidemia, diabetes, dialysis, smoking, asthma, and chronic obstructive pulmonary disease), laboratories upon admission (neutrophil and lymphocyte counts, lactate, C-reactive protein, D-dimer, bilirubin and serum creatinine), vital signs on presentation (pulse, blood pressure, SpO_2, respiratory rate and temperature) and the total dose of glucocorticoids administered. This scoring was used to inversely weight the probability of treatment group when analyzing the primary outcome of overall survival at 30 days. Next, Cox

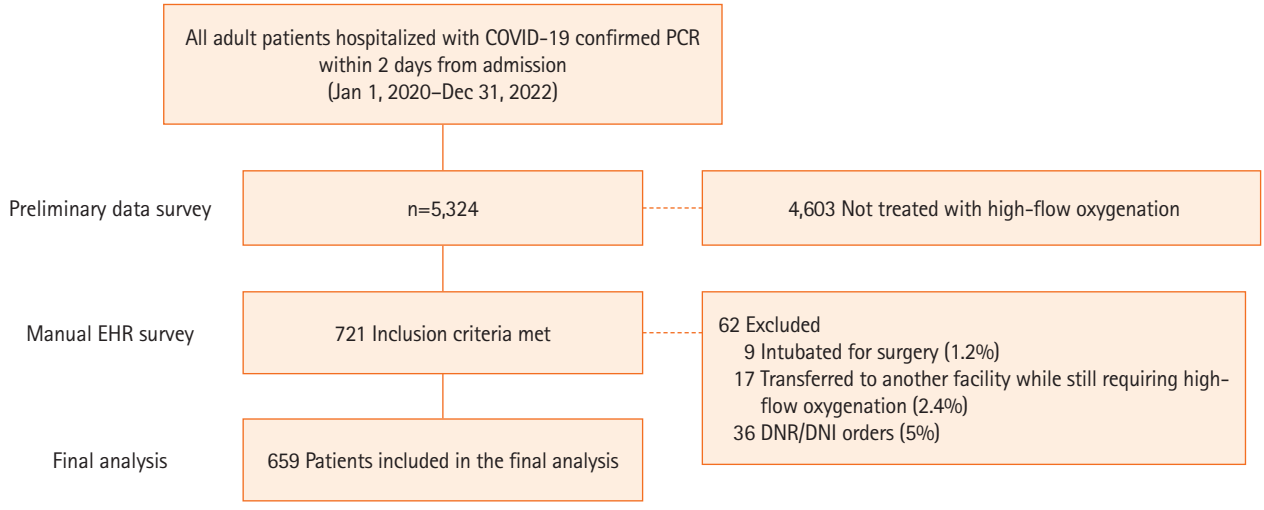

Figure 1. Flowchart of the study. COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction; DNR: do-not-resuscitate; DNI: do-not-intubate.

Table 1. Study patients characteristics

Variable	HFNC alone (control, n=343)	Dual (HFNC+RM, n=316)	P-value
Female	131 (38.2)	110 (34.8)	0.368
Age (yr)	66.5±15.6	68.0±15.7	0.198
History			
Solid malignancy	72 (20.9)	93 (29.4)	0.012
Hematological malignancy	24 (7.0)	39 (12.3)	0.020
Heart failure	103 (30.0)	135 (42.7)	0.001
Hemodialysis	21 (6.1)	32 (10.1)	0.059
COPD	31 (9.0)	23 (7.3)	0.411
Asthma	13 (3.8)	17 (5.4)	0.328
Smoking	43 (12.5)	48 (15.2)	0.324
Atrial fibrillation	50 (14.6)	58 (18.4)	0.191
Dyslipidemia	146 (42.6)	165 (52.2)	0.013
Hypertension	82 (23.9)	109 (34.5)	0.003
Ischemic heart disease	90 (26.2)	98 (31.0)	0.175
Diabetes mellitus	135 (39.4)	131 (41.5)	0.584
Laboratory results upon admission			
White blood cells ($x10^3$/μl)	3.8±7.4	5.6±12.9	0.019
Neutrophiles ($x10^3$/μl)	6.9±4.2	7.2±5.3	0.563
Lymphocytes ($x10^3$/μl)	1.9±14.2	2.3±13.3	0.779
Hemoglobin (mg/dl)	12.0±2.3	12.3±2.3	0.153
Lactate (mMol/L)	0.7±1.0	1.0±1.1	<0.001
C-reactive protein (mg/dl)	6.6±9.9	9.1±10.7	0.002
D-dimer (mg/ml)	1,321±1,083	1,489±1,182	0.198
Bilirubin (mg/dl)	0.6±0.4	0.6±0.6	0.420
Serum creatinine (mg/dl)	1.5±1.5	1.4±1.4	0.511
Glucocorticoid length of treatment (day)	5.9±3.8	6.0±3.7	0.882
Glucocorticoid cumulative dose (prednisone equivalent in mg)	237±153	238±148	0.879
Highest SOFA score during hospitalization	4.7±1.7	4.7±1.8	0.983
Highest ROX index within 12 hours from HFNC initiation	4.4±1.1	4.7±1.4	0.003
Body mass index (kg/m^2)	29.0±5.8	29.6±6.2	0.240
Day on HFNC	13 (4 to 22)	13 (4 to 24)	0.266
BiPAP	84 (24.5)	68 (21.5)	0.366
Day to BiPAP initiation	0 (0 to 4)	−1 (−2 to 2)	0.389
Day on BiPAP 3	3 (1 to 6)	3 (1 to 5)	0.635
Deceased 30 days after first application of HFNC	146 (42.6)	104 (32.9)	0.011
Intubated 30 days after first application of HFNC	65 (19)	46 (14.6)	0.132
Admitted to the ICU within 30 days after first application of HFNC	100 (29.2)	93 (29.3)	0.938

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
HFNC: high-flow nasal cannula; RM: reservoir mask; COPD: chronic obstructive pulmonary disease; SOFA: Sequential Organ Failure Assessment; ROX: respiratory rate oxygenation; BiPAP: bilevel positive airway pressure support; ICU: intensive care unit.

proportional weighted hazard model was constructed. Age, body mass index, highest SOFA score during hospitalization and ROX index at 6 hours after the initiation of HFNC were included in the model. Dual oxygenation remained an independent predictor of 30 days mortality (adjusted hazard ratio, 0.615; 95% confidence interval, 0.469–0.809), as presented in Supplementary Table 1. The inverse probability of treatment weighted survival is depicted in Figure 3.

DISCUSSION

Our study demonstrated a decreased 30 days mortality in patients treated with the addition of RM on top of HFNC. This association remained unchanged after accounting for multiple

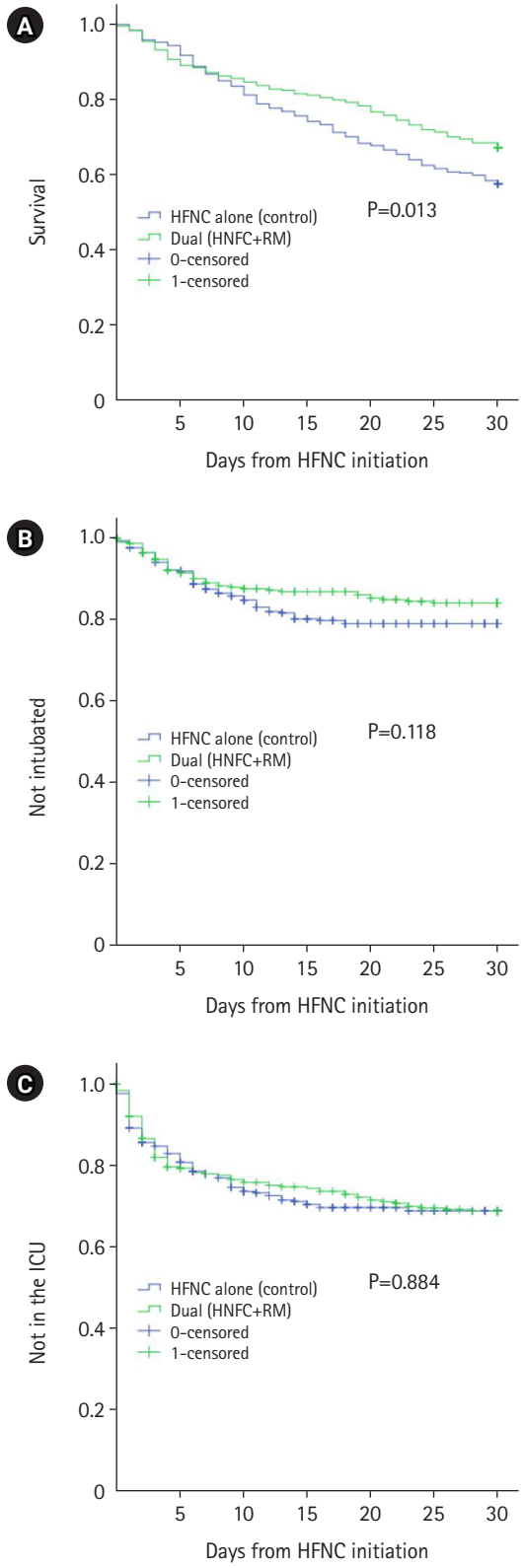

Figure 2. Kaplan-Mayer survival curves from first high-flow nasal cannula (HFNC) to death (A), the initiation of invasive positive pressure ventilation (i.e., intubation) (B), and admission to the intensive care unit (ICU) (C). RM: reservoir mask.

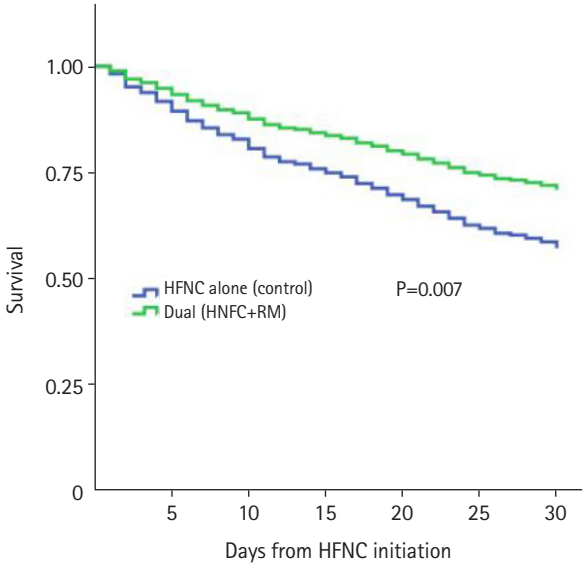

Figure 3. Propensity score weighted Cox regression for 30 days survival. Predicting variables included respiratory support method (dual vs. high-flow nasal cannula [HFNC] alone), age, respiratory rate oxygenation (ROX) index, Sequential Organ Failure Assessment score, and body mass index. RM: reservoir mask.

potential confounders, including age, smoking status, body mass index, underlying diseases (and particularly chronic lung diseases), laboratories and vital signs at presentation and severity as reflected by the SOFA score and ROX index. Several mechanistic explanations could be offered to elucidate these results.

First, flow addition might be of importance. While 40 L/min is much higher than the typical minute ventilation, this ventilatory volume is inspired over a period of time that is significantly shorter, leading to high-peak inspiratory flows (PIF). Patients in respiratory failure demonstrated PIFs of over 42 L/min on average and up to 120 L/min [11]. Conversely, the O_2 infrastructure in our hospital only allows for up to 40 L/min flow of pure oxygen, lower than the maximal flow of most available HFNC devices, that support minute flow of up to 60 L/min. In other words, 15 L/min of RM added to the HFNC of 40 L/min (increasing flow by 37.5) may be significant in view of the high PIF in respiratory failure [12,13]. In a recent bench and healthy volunteers model, increasing the flow from 40 to 60 also increased the positive end expiratory pressure, which might explain improved oxygenation [6].

Second, not unlike the addition of a surgical mask (shown in a small study to improve oxygenation) [10] or simply adding a venturi mask with no flow [14], the RM adds a physical barri-

er. All high flow devices in our center rely on nasal prongs for delivery. Shifts to the hemoglobin dissociation curve [15], and the rise of $PaCO_2$ [16] have all been suggested to explain these findings. It seems, nonetheless, that the most likely mechanism is the decrease of room air entrainment in the presence of a physical barrier. PEEP was significantly lowered when the subjects opened their mouths [6]—a posture typical of the air hungry patient. This was shown in volunteers subjected to strenuous exercise to simulate the increased ventilation in severe respiratory failure (shown to breathe through their mouth) [17]. Partial arterial pressure of O_2 was significantly increased (with $PaCO_2$ unchanged) when a barrier was applied [10]. FIO_2 delivery was shown to decrease significantly in severe respiratory failure, a finding attributed to room air entrainment, in a recent meta-analysis [18]. It seems the simple barrier of the RM helps funnel the high flow from the nasal prongs to the mouth, contributing especially in severe respiratory distress where patients are more likely to breathe with their mouth open.

The decrease in room air entrainment might be even more significant when a highly compliant reservoir is added [9]. The large diameter and proximity of the reservoir bag minimize the resistance of this source of effectively pure oxygen during inspiration [7]. Since, as discussed above, the limiting factor in respiratory failure seems to be flow rather than volume, even the modest volume (but high flow) reservoir bag could help address the increased PIF needs of patients with respiratory failure.

This study has several important limitations. Firstly, the retrospective design inherently raises the risk of biases, particularly since no randomization was performed and no strict protocol detailing the criteria for adding RM to HFNC was followed. As a result, criteria for adding RM or ICU admission varied greatly between physicians and during various phases of the pandemic, as did criteria for intubation or ICU admission. Secondly, no consistent data was available regarding important physiological parameters (oxygenation, respiratory effort, etc.) immediately before and after the addition of RM, leaving our inference of the mechanism by which this intervention improves oxygenation to be very limited, relying on previous much smaller studies. Similarly, we could not ascertain the extent and duration to which the patient's mouth was open. Lastly, mortality in this cohort was high. While sadly not atypical of the pandemic, such rates are not expected in all respiratory failure patients.

In conclusion, this study demonstrates the potential efficacy of the addition of RM on top of HFNC in COVID-19 patients with severe hypoxemia, resulting in improved overall survival. This cheap, widely available, and safe treatment may warrant further studies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: IG, RZ, EF. Methodology: IG. Formal analysis: IG. Data curation: IG, KH. Visualization: IG. Project administration: EF. Writing–original draft: IG, EF. Writing–review & editing: IG, RZ, KH, AN, EF.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.00451.

REFERENCES

1. Macedo A, Gonçalves N, Febra C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Ann Epidemiol 2021;57:14-21.
2. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. PLoS One 2020;15:e0241955.

3. Groff P, Ferrari R. Non-invasive respiratory support in the treatment of acute hypoxemic respiratory failure secondary to COVID-19 related pneumonia. Eur J Intern Med 2021;86:17-21.
4. Crimi C, Pierucci P, Renda T, Pisani L, Carlucci A. High-flow nasal cannula and COVID-19: a clinical review. Respir Care 2022;67:227-40.
5. Godoy DA, Graneros N, Oyarzabal L, Murillo-Cabezas F. High-flow oxygen therapy in acute hypoxemic respiratory failure secondary to COVID-19 pneumonia. Med Intensiva (Engl Ed) 2021;45:506-8.
6. Vieira F, Bezerra FS, Coudroy R, Schreiber A, Telias I, Dubo S, et al. High-flow nasal cannula compared with continuous positive airway pressure: a bench and physiological study. J Appl Physiol (1985) 2022;132:1580-90.
7. Gur I, Zalts R, Azzam M, Hussein K, Neuberger A, Fuchs E. Dual oxygenation in the treatment of hypoxemic respiratory failure: a retrospective cohort study. Isr Med Assoc J 2023;25:595-600.
8. Leeies M, Flynn E, Turgeon AF, Paunovic B, Loewen H, Rabbani R, et al. High-flow oxygen via nasal cannulae in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. Syst Rev 2017;6:202.
9. Duprez F, Bruyneel A, Machayekhi S, Droguet M, Bouckaert Y, Brimioulle S, et al. The double-trunk mask improves oxygenation during high-flow nasal cannula therapy for acute hypoxemic respiratory failure. Respir Care 2019;64:908-14.
10. Montiel V, Robert A, Robert A, Nabaoui A, Marie T, Mestre NM, et al. Surgical mask on top of high-flow nasal cannula improves oxygenation in critically ill COVID-19 patients with hypoxemic respiratory failure. Ann Intensive Care 2020;10:125.
11. Mälberg J, Hadziosmanovic N, Smekal D. Physiological respiratory parameters in pre-hospital patients with suspected COVID-19: a prospective cohort study. PLoS One 2021;16:e0257018.
12. Duprez F, de Terwangne C, Bellemans V, Poncin W, Reychler G, Sorgente A, et al. High-flow nasal cannula therapy, factors affecting effective inspired oxygen fraction: an experimental adult bench model. J Clin Monit Comput 2022;36:1441-8.
13. Mauri T, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med 2017;43:1453-63.
14. Dogani B, Månsson F, Resman F, Hartman H, Tham J, Torisson G. The application of an oxygen mask, without supplemental oxygen, improved oxygenation in patients with severe COVID-19 already treated with high-flow nasal cannula. Crit Care 2021;25:319.
15. Born P, Castro R. A combination of Bohr and Haldane effects provide a physiologic explanation for the increase in arterial oxygen saturation when a face mask is added to a high-flow nasal cannula in severely hypoxemic COVID-19 patients. Crit Care 2021;25:395.
16. Swenson ER. Does inspiration of exhaled CO2 explain improved oxygenation with a face mask plus high-flow nasal cannula oxygen in severe COVID-19 infection? Crit Care 2021;25:343.
17. Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care 2011;39:1103-10.
18. Lee CC, Mankodi D, Shaharyar S, Ravindranathan S, Danckers M, Herscovici P, et al. High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: a systematic review. Respir Med 2016;121:100-8.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):442-451
https://doi.org/10.4266/acc.2023.00682

| pISSN 2586-6052 | eISSN 2586-6060

Risk factors for mortality in intensive care unit patients with *Stenotrophomonas maltophilia* pneumonia in South Korea

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Background: *Stenotrophomonas maltophilia* has been increasingly recognized as an opportunistic pathogen associated with high morbidity and mortality. Data on the prognostic factors associated with *S. maltophilia* pneumonia in patients admitted to intensive care unit (ICU) are lacking.
Methods: We conducted a retrospective analysis of data from 117 patients with *S. maltophilia* pneumonia admitted to the ICUs of two tertiary referral hospitals in South Korea between January 2011 and December 2022. To assess risk factors associated with in-hospital mortality, multivariable logistic regression analyses were performed.
Results: The median age of the study population was 71 years. Ventilator-associated pneumonia was 76.1% of cases, and the median length of ICU stay before the first isolation of *S. maltophilia* was 15 days. The overall in-hospital mortality rate was 82.1%, and factors independently associated with mortality were age (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.00–1.09; P=0.046), Sequential Organ Failure Assessment (SOFA) score (OR, 1.21; 95%; CI, 1.02–1.43; P=0.025), corticosteroid use (OR, 4.19; 95% CI, 1.26–13.91; P=0.019), and polymicrobial infection (OR, 95% CI 0.07–0.69). However, the impact of appropriate antibiotic therapy on mortality was insignificant. In a subgroup of patients who received appropriate antibiotic therapy (n=58), antibiotic treatment modality-related variables, including combination or empirical therapy, also showed no significant association with survival.
Conclusions: Patients with *S. maltophilia* pneumonia in ICU have high mortality rates. Older age, higher SOFA score, and corticosteroid use were independently associated with increased in-hospital mortality, whereas polymicrobial infection was associated with lower mortality. The effect of appropriate antibiotic therapy on prognosis was insignificant.

Key Words: anti-bacterial agents; intensive care units; pneumonia; risk factors; *Stenotrophomonas maltophilia*

Original Article

Received: May 9, 2023
Revised: August 22, 2023
Accepted: September 27, 2023

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INTRODUCTION

Stenotrophomonas maltophilia is a Gram-negative multidrug-resistant bacterium that has

emerged as a significant opportunistic pathogen of global concern [1]. *S. maltophilia* infections primarily present as a respiratory tract infection, with significant morbidity in vulnerable patients, including immunocompromised and debilitated patients [2]. Varying degrees of mortality have been reported in patients with *S. maltophilia* pneumonia, with rates reaching as high as 70% [2]. Owing to intrinsic resistance to various antibiotics, limitations in antimicrobial susceptibility testing (AST), and lack of clinical data, the treatment of *S. maltophilia* infection is a significant challenge for clinicians [3].

Factors commonly encountered in patients admitted to intensive care unit (ICU), such as severe illness, invasive procedures, and exposure to broad-spectrum antibiotics, have been reported to be associated with ICU-acquired *S. maltophilia* pneumonia, which is a significant risk factor for ICU death [4]. Previous studies have shown that the frequency of *S. maltophilia* pneumonia in ICU tends to increase over time [4]; moreover, in a recent study on patients with pneumonia in ICUs of medical centers in the United States, *S. maltophilia* was one of the top six commonly identified pathogens [5]. Additionally, there has been an increase in resistance rates to drugs that have classically shown good susceptibility [3]. Despite this emerging clinical relevance, *S. maltophilia* has been considerably less studied than other Gram-negative bacteria [3], and clinical data on *S. maltophilia* pneumonia in the ICU setting are lacking.

In the present study, we aimed to retrospectively analyze patients with *S. maltophilia* pneumonia in the ICU to describe their clinical features and investigate factors, including antibiotic therapy, associated with mortality.

KEY MESSAGES

- In critically ill patients with *Stenotrophomonas maltophilia* pneumonia, older age, higher Sequential Organ Failure Assessment (SOFA) score, and corticosteroid use were associated with increased mortality, whereas polymicrobial infection was associated with better prognosis.
- The effect of appropriate antibiotic therapy on mortality was insignificant.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of each institution, which waived the requirement for informed consent owing to the retrospective nature of the study.

Study Design and Participants

This retrospective study was conducted at two tertiary referral centers, the Kyungpook National University Hospital and the Kyungpook National University Chilgok Hospital, in Daegu, Korea. Information on consecutive adult patients admitted to the ICUs, including both medical and surgical ICUs, at two hospitals between January 1, 2011, and December 31, 2022, was collected, and patients with *S. maltophilia* cultured from respiratory specimens during their ICU stay were selected. The exclusion criteria included patients with no pneumonia events throughout their stay in the ICU, those who died or were discharged on the day of specimen collection, those with inadequate specimens, and those with *S. maltophilia* colonization (Figure 1). Clinical features were compared by dividing patients into two groups based on the occurrence of in-hospital death, which is the outcome of interest in the current study.

Definitions

S. maltophilia pneumonia was diagnosed when there was a positive microbiologic culture from a respiratory specimen and concurrent clinical and radiological signs consistent with pneumonia, defined as new or progressive lung infiltrates on chest radiograph plus at least two of the following clinical criteria: (1) body temperature of >38.0 °C or <36.0 °C, (2) white blood cell count of ≥12,000/mm^3 or ≤4,000/mm^3, and (3) macroscopically purulent tracheal aspirate or sputum, referring to some of the criteria proposed by U.S. Centers for Disease

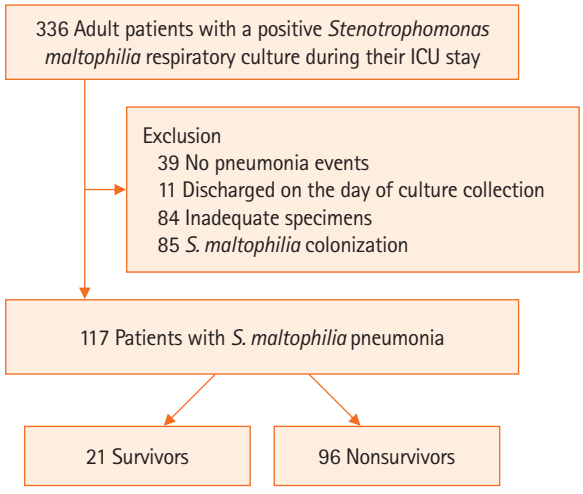

Figure 1. Flowchart of the study. ICU: intensive care unit.

Control and Prevention [6]. Cases with a positive respiratory sample but not meeting the abovementioned pneumonia criteria were considered as *S. maltophilia* colonization and excluded from the final analysis. Ventilator-associated pneumonia (VAP) was defined as pneumonia in patients who had received at least 48 hours of mechanical ventilation [7]. The respiratory specimen was considered to be adequate with the following threshold: (1) quantitative culture of bronchoalveolar lavage (≥10^4 colony-forming unit [CFU]/mL), (2) quantitative culture of bronchoscopic or endotracheal aspirates (≥10^5 CFU/mL), (3) semi-quantitative culture of endotracheal aspirates (moderate or higher), or (4) sputum with <10 epithelial cells in a low power field.

Immunosuppression was defined as patients with at least one of the following: neutropenia (absolute neutrophil count or total white blood cell count of <500/mm^3), hematologic malignancy or human immunodeficiency virus positive with CD4 count of <200, a history of splenectomy, solid organ or hematopoietic stem cell transplant, cytotoxic chemotherapy, immunosuppressant, or receiving daily corticosteroid therapy with a dose of ≥20 mg of prednisone or equivalent for ≥14 days) [6,8]. Polymicrobial infection was defined as the detection of other bacteria at the same time as the first isolation of *S. maltophilia* or within 1 week thereafter. Corticosteroid administration was referred to as at least one dose of ≥10 mg of prednisone or equivalent within the same time frame (within 1 week of index culture collection).

Appropriate antibiotic therapy was defined as a case where at least one antibiotic showing sensitivity in the AST was administered for 48 hours or longer, and simultaneous administration of two or more antibiotics was referred to as combination therapy. Among patients who received appropriate antibiotic therapy, those who started treatment before *S. maltophilia* was first identified were defined as empiric therapy, and the remaining cases were defined as definitive therapy.

Data Collection

Patients' baseline characteristics, including demographics, comorbid conditions, and laboratory test results, were obtained from electronic medical records. Prior antibiotic exposure within the last 90 days was investigated, and variables indicative of severity at the time of admission to ICU, including Acute Physiological and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, were reviewed. The use of vasopressors prior to *S. maltophilia* infection was recorded.

To evaluate the severity of illness at the beginning of *S. maltophilia* infection, SOFA scores on the day of index culture collection were examined. For several drugs, AST results of the identified strains were recorded. Information on the presence of polymicrobial infection and isolation of *S. maltophilia* from normally sterile sites, including blood, abdominal fluid, pleural fluid, and cerebrospinal fluid, was collected. Moreover, the frequency of corticosteroid administration was recorded.

In addition to appropriate antibiotic therapy, the following variables related to treatment were investigated: monotherapy; combination therapy; use of trimethoprim-sulfamethoxazole (TMP-SMX), levofloxacin, and minocycline; empiric therapy; definitive therapy; and time interval from *S. maltophilia* diagnosis to initiation of appropriate antibiotics.

Statistical Analysis

Continuous variables were expressed as medians (interquartile range [IQR]), whereas categorical variables were expressed as numbers (percentage). Comparisons between two groups were performed using Mann-Whitney U-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. To investigate the independent factors associated with in-hospital death, a multivariable analysis was performed using a logistic regression model. Variables showing statistically significant differences between the groups in univariate analysis or those considered clinically significant were subjected to multivariable analysis, and the backward elimination method was used to define the independent risk factors. Statistical analysis was performed using RStudio (R version 4.2.1). Two-sided P-value of <0.05 was considered to indicate statistically significant.

RESULTS

Initially, 336 patients with a positive *S. maltophilia* respiratory culture during their ICU stay were identified. Among them, those with no pneumonia events throughout their ICU stay (n=39), those who died or were discharged on the day of culture collection (n=11), those with inadequate specimens (n=84), and those with *S. maltophilia* colonization (n=85) were excluded. Subsequently, the data of 117 patients were analyzed. *S. maltophilia* was cultured from endotracheal aspirate (n=107), bronchoalveolar lavage (n=5), and sputum (n=5), with 4 cases additionally displaying concurrent bacteremia. The overall in-hospital mortality rate was 82.1% (n=96). The median duration of mechanical ventilation for all patients was

22 days, with no significant difference between the in-hospital survivors and nonsurvivors (median [IQR], 28 days [12–40] vs. 20 days [9–35]; P=0.146).

Baseline Characteristics

The baseline and clinical characteristics of patients are presented in Table 1. The median age of the study population was 71 years, which was significantly lower in survivors than in nonsurvivors (median [IQR], 64 years [55–72] vs. 72 years [65–80]; P=0.027). Comorbid conditions and prior antibiotic exposure were comparable between the two groups. The median APACHE II and SOFA scores of all patients at ICU admission were 17 and 8, respectively, with no significant difference between the two groups. Initial laboratory test results were similar between the two groups, except for the levels of lactic acid (1.4 mmol/L [1.2–3.1] vs. 3.0 mmol/L [1.7–6.0]; P=0.033) (Table 2).

Variables Related to *S. maltophilia* Infection and Treatment Details

Variables related to *S. maltophilia* infection and its treatment details are displayed in Table 3. VAP accounted for 76.1% (n=89) of all patients, and the median length of ICU stay before the first isolation of *S. maltophilia* was 15 days, with no significant difference between the groups. Additionally, SOFA scores on the day of the first *S. maltophilia* culture collection were comparable between the groups. Survivors had a significantly higher frequency of polymicrobial infection than nonsurvivors (n=15 [71.4%] vs. n=32 [33.3%]; P=0.003).

Among patients with corticosteroid administration, the number of survivors was significantly lower than that of nonsurvivors (n=5 [23.8%] vs. n=50 [52.1%]; P=0.035). No signif-

Table 1. Demographic and baseline characteristics

Variable	Total (n=117)	Survivor (n=21)	Nonsurvivor (n=96)	P-value
Age (yr)	71 (63–78)	64 (55–72)	72 (65–80)	0.027
Male	75 (64.1)	13 (61.9)	62 (64.6)	>0.999
Body mass index (kg/m^2)	22.8 (19.8–25.0)	22.5 (20.1–24.2)	22.8 (19.8–25.1)	0.577
Comorbid condition				
Chronic pulmonary disease	18 (15.4)	3 (14.3)	15 (15.6)	>0.999
Hypertension	55 (47.0)	10 (47.6)	45 (46.9)	>0.999
Diabetes mellitus	39 (33.3)	7 (33.3)	32 (33.3)	>0.999
Cardiovascular disease	22 (18.8)	6 (28.6)	16 (16.7)	0.339
Cerebrovascular disease	14 (12.0)	2 (9.5)	12 (12.5)	0.992
Chronic kidney disease	20 (17.1)	2 (9.5)	18 (18.8)	0.486
Chronic liver disease	2 (1.7)	0	2 (2.1)	>0.999
Connective tissue disease	3 (2.6)	0	3 (3.1)	0.953
Cancer	28 (23.9)	2 (9.5)	26 (27.1)	0.154
Immunosuppression	20 (17.1)	1 (4.8)	19 (19.8)	0.181
Previous antibiotic exposure				
Antipseudomonal penicillin or cephalosporin	41 (35.0)	5 (23.8)	36 (37.5)	0.348
Carbapenem	34 (29.1)	4 (19.0)	30 (31.2)	0.395
Aminoglycosides	5 (4.3)	2 (9.5)	3 (3.1)	0.473
Fluoroquinolones	29 (24.8)	4 (19.0)	25 (26.0)	0.694
Glycopeptides	28 (23.9)	3 (14.3)	25 (26.0)	0.389
Reason for ICU admission				
Medical condition	106 (90.6)	19 (90.5)	87 (90.6)	>0.999
Postoperative care	11 (9.4)	2 (9.5)	9 (9.4)	>0.999
Severity score on ICU admission				
APACHE II	17 (14–22)	16 (14–20)	18 (14–23)	0.362
SOFA	8 (5–10)	7 (4–9)	8 (5–11)	0.235
Vasopressor use	102 (87.2)	18 (85.7)	84 (87.5)	>0.999

Values are presented as median (interquartile range) or number (%).
ICU: intensive care unit; APACHE: Acute Physiological and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

Table 2. Initial laboratory findings

Variable	n	Total	Survivor (n=21)	Nonsurvivor (n=96)	P-value
White blood cell (×10^3/L)	117	11.5 (7.6–16.3)	11.2 (6.7–21.0)	11.6 (7.8–15.6)	0.607
Neutrophil–lymphocyte ratio	116	11.9 (5.0–24.2)	8.7 (5.3–32.9)	13.4 (4.8–23.9)	>0.999
Hematocrit (%)	117	32.1 (28.1–36.9)	33.0 (29.6–36.4)	31.8 (27.8–37.0)	0.486
C-reactive protein (mg/dl)	115	9.3 (2.8–19.2)	10.7 (1.4–19.1)	9.2 (3.7–19.3)	0.612
Albumin (g/dl)	116	2.8 (2.5–3.2)	2.6 (2.1–3.2)	2.8 (2.5–3.2)	0.143
Procalcitonin (mmol/L)	64	0.8 (0.2–6.9)	0.7 (0.3–6.2)	0.8 (0.2–7.5)	0.877
LDH (U/L)	63	495 (323–750)	445 (247–518)	514 (335–886)	0.105
Lactic acid (mmol/L)	65	2.6 (1.6–5.5)	1.4 (1.2–3.1)	3.0 (1.7–6.0)	0.033
D-dimer (μg/ml)	70	7.3 (3.7–19.8)	7.3 (5.4–10.9)	7.5 (3.0–20.0)	>0.999
Ferritin (ng/ml)	24	839.7 (277.2–1,481.3)	871.5 (689.7–923.0)	709.2 (221.2–1,903.0)	0.970

Values are presented as median (interquartile range).
LDH: lactate dehydrogenase.

Table 3. Variables regarding *Stenotrophomonas maltophilia* infection and treatment details

Variable	Total (n=117)	Survivor (n=21)	Nonsurvivor (n=96)	P-value
Ventilator-associated pneumonia	89 (76.1)	15 (71.4)	74 (77.1)	0.789
Length of ICU stay before *S. maltophilia* infection (day)	15 (10–27)	16 (10–30)	15 (10–27)	0.935
SOFA score on the day of index culture collection	7 (5–10)	7 (4–9)	7 (5–12)	0.131
Polymicrobial infection	47 (40.2)	15 (71.4)	32 (33.3)	0.003
S. maltophilia isolation from normally sterile sites[a)]	10 (8.5)	1 (4.8)	9 (9.4)	0.799
Corticosteroid use	55 (57.0)	5 (23.8)	50 (52.1)	0.035
Appropriate antibiotic therapy	58 (49.6)	10 (47.6)	48 (50.0)	>0.999
Monotherapy	48 (41.0)	9 (42.9)	39 (40.6)	>0.999
Combination therapy	10 (8.5)	1 (4.8)	9 (9.4)	0.799
Empiric therapy	18 (15.4)	2 (9.5)	16 (16.7)	0.626
Definitive therapy	40 (34.2)	8 (38.1)	32 (33.3)	0.871
Time interval between *S. maltophilia* isolation and antibiotic treatment (day)	1 (0–4)	1 (0–4)	0 (0–4)	0.417
TMP–SMX use	20 (17.1)	3 (14.3)	17 (17.7)	0.954
Levofloxacin use	37 (31.6)	6 (28.6)	31 (32.3)	0.942
Minocycline use	18 (15.4)	2 (9.5)	16 (16.7)	0.626

Values are presented as number (%) or median (interquartile range).
ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; TMP–SMX: trimethoprim–sulfamethoxazole.
a) Including blood, abdominal fluid, pleural fluid, and cerebrospinal fluid.

icant differences were observed between the two groups in terms of antibiotic treatment modality-related variables and appropriate antibiotic therapy.

Antibiotic Susceptibility

For the four main drugs, AST results of 115 patients are depicted in Figure 2A. The proportion of cases susceptible to TMP– SMX was the highest at 92.2%, followed by that of cases susceptible to levofloxacin (59.1%), minocycline (41.7%), and ceftazidime (20%). The proportion of cases showing resistant or intermediate results were for ceftazidime and levofloxacin was 48.7% and 24.4%, respectively, which tended to be higher than that of cases showing resistant or intermediate results for TMP–SMX (7.8%) and minocycline (4.3%).

Polymicrobial Infections

In 40.2% (n=47) of patients, other microorganisms were identified at the time of *S. maltophilia* isolation or within the first week of isolation. The distribution of coisolates is depicted in Figure 2B. *Acinetobacter* species showed the highest frequency (n=19), followed by *Staphylococcus aureus* (n=10), *Klebsiella pneumoniae* (n=10), and *Pseudomonas aeruginosa* (n=9).

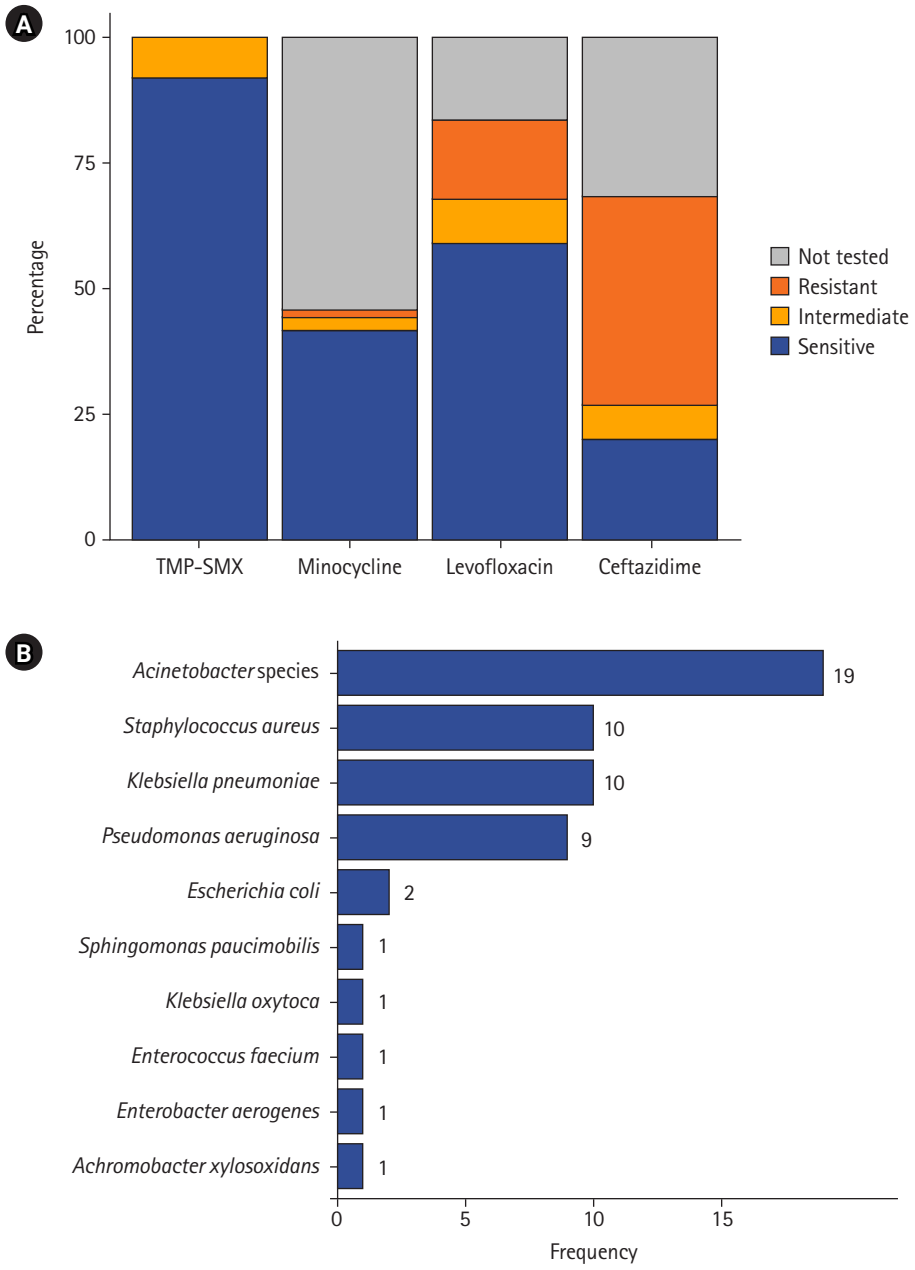

Figure 2. (A) Antibiotic susceptibility of *Stenotrophomonas maltophilia* strains isolated from the respiratory tract specimen of critically ill patients (n=115). Susceptibility results for each antibiotic are expressed as a percentage of all cases. (B) Frequency distribution of coisolates in patients with polymicrobial infection (n=47). Results are sorted by frequency, with duplicates allowed. TMP–SMX: trimethoprim–sulfamethoxazole.

Escherichia coli was isolated in two cases, and *Sphingomonas paucimobilis*, *Klebsiella oxytoca*, *Enterococcus faecium*, *Enterobacter aerogenes*, and *Achromobacter xylosoxidans* were isolated in one case each.

Risk Factors Associated with In-Hospital Mortality

The following factors were included in the multivariable analysis: age, APACHE II, vasopressor use, SOFA score on the day of index culture collection, polymicrobial infection, corticosteroid use, and appropriate antibiotic therapy. Consequently, age (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.00–1.09; P=0.046), SOFA score (OR, 1.21; 95%; CI, 1.02–1.43; P=0.025), corticosteroid use (OR, 4.19; 95% CI, 1.26–13.91; P=0.019) and polymicrobial infection (OR, 0.22; 95% CI,

Table 4. Variables associated with in-hospital death assessed via multivariable logistic regression analysis

Variable	Univariate analysis			Multivariable analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (yr)	1.04	1.00–1.09	0.043	1.05	1.00–1.09	0.046
APACHE II score	1.04	0.97–1.12	0.300			
Vasopressor use	1.17	0.25–4.14	0.800			
SOFA score on the day of index culture collection	1.13	0.99–1.30	0.082	1.21	1.02–1.43	0.025
Polymicrobial infection	0.20	0.07–0.54	0.002	0.22	0.07–0.69	0.009
Corticosteroid use	3.48	1.25–11.3	0.024	4.19	1.26–13.91	0.019
Appropriate antibiotic therapy	1.10	0.43–2.87	0.800			

OR: odds ratio; CI: confidence interval; APACHE: Acute Physiological and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

0.07–0.69; P=0.009) were independent factors associated with in-hospital death, whereas appropriate antibiotic therapy did not modify mortality (Table 4).

A multivariable analysis performed in a subgroup of patients who received appropriate antibiotic therapy (n=58) showed that vasopressor use (P=0.044), polymicrobial infection (P=0.025), and corticosteroid use (P=0.046) were associated with in-hospital mortality. However, additionally included antibiotic treatment modality-related variables such as combination, empirical treatment, time interval from *S. maltophilia* diagnosis to initiation of appropriate antibiotics, and use of specific antibiotics, had no significant effect on survival (Supplementary Table 1).

In addition, a subgroup analysis was conducted for patients receiving corticosteroids (n=55). At the start of corticosteroid treatment, methylprednisolone was the most frequently prescribed, accounting for over half (56.4%) of cases, and it was administered at a median daily dosage of 0.9 mg/kg. Septic shock was the most common reason for corticosteroid use, followed by acute respiratory distress syndrome and severe pneumonia (Supplementary Table 2). The same multivariable analysis was performed including the aforementioned factors in this subgroup, but no statistically significant prognostic factors were found (Supplementary Table 3).

DISCUSSION

In this cohort of 117 critically ill patients with *S. maltophilia* pneumonia, the in-hospital mortality rate was approximately 82%. Factors that were independently associated with in-hospital death were age, SOFA score, corticosteroid use, and polymicrobial infection. However, the effects of appropriate antibiotic therapy, as well as empiric or combination therapy, on mortality were not significant.

Previous studies on critically ill patients with *S. maltophilia* pneumonia have reported hospital or ICU mortality rates of approximately 50%–70% [9-13], which are mostly lower than those of our study patients. Although the high mortality rate in the present study cannot be clearly explained by our data alone, it may be attributed to the fact that our patients had a median age of 71 years, surpassing the median age range of 61 to 65 years in previous studies [9,11-13]. While not identified as a prognostic factor in our study, the comparatively lower proportion of patients (49.6%) receiving appropriate antibiotic therapy, in contrast to the approximately 60%–73% range reported in prior studies [9-11,13], could have also exerted an influence. Furthermore, the outcomes of the current study might have been adversely influenced by the incorporation of patients with *S. maltophilia* pneumonia, using comparatively stringent criteria that eliminated colonization cases. This is in contrast to earlier studies which encompassed not only *S. maltophilia* infections but also instances of colonization [10,12].

As a general treatment approach for *S. maltophilia* infections, antibiotics including TMP–SMX, minocycline, and levofloxacin, are recommended as monotherapy or combination therapy depending on severity; however, there are limited clinical data to strongly support a specific treatment strategy [14]. In particular, data on the impact of appropriate antibiotic therapy on the prognosis of relatively severe *S. maltophilia* pneumonia in ICU are lacking, and most studies show conflicting results [9,13,15]. In a study including patients with VAP caused by *S. maltophilia*, Ibn Saied et al. [13] reported that adequate treatment did not improve prognosis, which is similar to our study finding, whereas other studies involving critically ill patients with *S. maltophilia* pneumonia showed a significant association between appropriate antibiotic therapy and reduced mortality [9,15]. Regarding antibiotic treatment modalities,

neither empiric nor combination therapy had a significant effect on survival in the current study, which is consistent with several recent studies [9,11,13].

In agreement with previous studies [9,11,12], compared with other antibiotics, *S. maltophilia* strains in our study showed the highest percentage of susceptibility in TMP–SMX. Moreover, the study by Puech et al. proposed TMP-SMX as the only agent with a survival benefit in patients with VAP caused by *S. maltophilia*. However, our study did not identify a benefit in terms of clinical outcomes for any particular antibiotic. Since there are data showing favorable outcomes related to adequate antibiotics in critically ill patients with *S. maltophilia* pneumonia [9,15], the need for appropriate antibiotic therapy cannot be denied in clinical practice; however, our findings suggest a more conservative approach to antibiotic treatment strategy rather than preemptive administration of a specific antibiotic before confirming AST results or the combination of two or more drugs.

In our study, a higher SOFA score was one of the predictors of mortality. This finding is consistent with previous data, wherein the SOFA score on the day of pneumonia onset or *S. maltophilia* isolation was independently associated with mortality of *S. maltophilia* infection in the ICU setting [9,11,12]. These results, combined with the fact that antibiotic treatment targeting *S. maltophilia* did not modify the survival of our patients, may support the idea that *S. maltophilia* isolation represents a precarious underlying condition with a poor prognosis, rather than being highly virulent per se [11,16].

Corticosteroids were administered at a significantly higher rate to nonsurvivors compared to survivors in the present study. The effect of corticosteroids has not been reported in previous studies of critically ill patients with *S. maltophilia* pneumonia. Corticosteroid therapy could be considered an adjunctive treatment option in some severe cases for various indications [17-19]. However, the benefits and harms of corticosteroids seem to be inconsistent depending on the specific causative agent of pneumonia [20-22]. Based on our findings, we suggest that corticosteroids be used cautiously and only when essential in patients in the ICU with suspected or diagnosed *S. maltophilia* pneumonia. However, notably, this retrospective study may have a bias, including a higher use of corticosteroids in more severe cases such as shock and respiratory failure. Therefore, the significance of corticosteroid use in our findings requires caution in interpretation, and future well-designed prospective studies on this topic are warranted.

In our study, polymicrobial infection was another prognostic factor, associated with reduced in-hospital mortality. The reported proportion of polymicrobial infection in cohorts of critically ill patients with *S. maltophilia* is slightly higher than ours, ranging from 45% to 58% [9,11,12]. Its prognostic relevance seems to be inconsistent with our results, with some studies showing no significant difference between mono and polymicrobial infection in terms of mortality [9,11] and one study presenting a worse prognosis in patients with polymicrobial infection [12]. Given the heterogeneity in the type and distribution of coisolates in those studies [9,11,12] and the potential interactions between *S. maltophilia* and certain strains [23,24], clearly elucidating the significance of polymicrobial infection as a prognostic factor in critically ill patients with *S. maltophilia* based on the current small-scale study is difficult. Conversely, a recent study on multidrug-resistant *Acinetobacter baumannii* VAP reported a similar result to ours, which showed a lower mortality rate in the case of polymicrobial infection than that in monomicrobial, and the attenuation of virulence due to competition with coexisting pathogens in a polymicrobial setting was suggested as a possible explanation [25].

Taken together, our results suggest that when *S. maltophilia* pneumonia is suspected in an ICU environment, high-risk patients, including those with older age and high severity scores, should be carefully screened and reevaluated for excessive use of antibiotics or corticosteroids. Furthermore, considering the high mortality rate of such patients and unknown efficacy of appropriate antibiotic therapy, various measures for preventing *S. maltophilia* infection and transmission, including barrier precautions during patient care, antibiotic stewardship, and appropriate maintenance of hospital environment and medical equipment [2], should be meticulously implemented.

The present study has several limitations. Considering the retrospective nature of this study, there may have been biases that were not identified. First of all, it should be considered that not all of the *S. maltophilia* pneumonia defined in our study may represent true infections. Approximately 40% of cases in our study had polymicrobial infections, with coisolates varying in species and frequency. Even after adjustment for polymicrobial infection, detailed information on antibiotics susceptibility testing or targeted antibiotic therapy for coisolates was not obtained. Furthermore, in such cases with polymicrobial infections, it is difficult to determine which microorganism is the actual causative agent of pneumonia. This may have influenced our results, where appropriate antibiotic therapy was not associated with mortality. Second, the presence of acute

illness in organs other than the lungs during ICU stay was not considered in our analysis. Third, although steroid treatment was a prognostic factor in this study, we evaluated steroid use in a relatively narrow window of time: within the first week of index culture collection. Corticosteroids administered during other periods may also have affected clinical outcomes. Another limitation is that this study was conducted with a limited number of patients at institutions located in a single region. In addition, the smaller size of the subgroups may have compromised the reliability of our results.

In conclusion, patients with *S. maltophilia* pneumonia in ICU settings have high mortality rates. Older age, higher SOFA score, and corticosteroid use were independently associated with increased in-hospital mortality, whereas polymicrobial infection was associated with lower mortality. The effect of appropriate antibiotic therapy on the prognosis was not significant.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.00682.

REFERENCES

1. Brooke JS. Advances in the microbiology of Stenotrophomonas maltophilia. Clin Microbiol Rev 2021;34:e0003019.
2. Looney WJ, Narita M, Mühlemann K. Stenotrophomonas maltophilia: an emerging opportunist human pathogen. Lancet Infect Dis 2009;9:312-23.
3. Mojica MF, Humphries R, Lipuma JJ, Mathers AJ, Rao GG, Shelburne SA, et al. Clinical challenges treating Stenotrophomonas maltophilia infections: an update. JAC Antimicrob Resist 2022;4:dlac040.
4. Wang N, Tang C, Wang L. Risk factors for acquired Stenotrophomonas maltophilia pneumonia in intensive care unit: a systematic review and meta-analysis. Front Med (Lausanne) 2022;8:808391.
5. Sader HS, Castanheira M, Mendes RE, Flamm RK. Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015-17). J Antimicrob Chemother 2018;73:3053-9.
6. Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN) patient safety component manual: Chapter 6. Pneumonia (ventilator-associated [VAP] and non-ventilator-associated pneumonia [PNEU]) event [Internet]. Centers for Disease Control and Prevention; 2023 [cited 2023 May 7]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf
7. Mietto C, Pinciroli R, Patel N, Berra L. Ventilator associated pneumonia: evolving definitions and preventive strategies. Respir Care 2013;58:990-1007.
8. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44-100.
9. Puech B, Canivet C, Teysseyre L, Miltgen G, Aujoulat T, Caron

M, et al. Effect of antibiotic therapy on the prognosis of ventilator-associated pneumonia caused by Stenotrophomonas maltophilia. Ann Intensive Care 2021;11:160.
10. Nseir S, Di Pompeo C, Brisson H, Dewavrin F, Tissier S, Diarra M, et al. Intensive care unit-acquired Stenotrophomonas maltophilia: incidence, risk factors, and outcome. Crit Care 2006;10:R143.
11. Guerci P, Bellut H, Mokhtari M, Gaudefroy J, Mongardon N, Charpentier C, et al. Outcomes of Stenotrophomonas maltophilia hospital-acquired pneumonia in intensive care unit: a nationwide retrospective study. Crit Care 2019;23:371.
12. Saugel B, Eschermann K, Hoffmann R, Hapfelmeier A, Schultheiss C, Phillip V, et al. Stenotrophomonas maltophilia in the respiratory tract of medical intensive care unit patients. Eur J Clin Microbiol Infect Dis 2012;31:1419-28.
13. Ibn Saied W, Merceron S, Schwebel C, Le Monnier A, Oziel J, Garrouste-Orgeas M, et al. Ventilator-associated pneumonia due to Stenotrophomonas maltophilia: risk factors and outcome. J Infect 2020;80:279-85.
14. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of AmpC β-lactamase-producing Enterobacterales, carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. Clin Infect Dis 2022;74:2089-114.
15. Hanes SD, Demirkan K, Tolley E, Boucher BA, Croce MA, Wood GC, et al. Risk factors for late-onset nosocomial pneumonia caused by Stenotrophomonas maltophilia in critically ill trauma patients. Clin Infect Dis 2002;35:228-35.
16. Pathmanathan A, Waterer GW. Significance of positive Stenotrophomonas maltophilia culture in acute respiratory tract infection. Eur Respir J 2005;25:911-4.
17. Ceccato A, Russo A, Barbeta E, Oscanoa P, Tiseo G, Gabarrus A, et al. Real-world corticosteroid use in severe pneumonia: a propensity-score-matched study. Crit Care 2021;25:432.
18. Yoshihiro S, Hongo T, Ohki S, Kaneko T, Ishikawa J, Ihara S, et al. Steroid treatment in patients with acute respiratory distress syndrome: a systematic review and network meta-analysis. J Anesth 2022;36:107-21.
19. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
20. Ding L, Huang H, Wang H, He H. Adjunctive corticosteroids may be associated with better outcome for non-HIV Pneumocystis pneumonia with respiratory failure: a systemic review and meta-analysis of observational studies. Ann Intensive Care 2020;10:34.
21. Moreno G, Rodríguez A, Reyes LF, Gomez J, Sole-Violan J, Díaz E, et al. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. Intensive Care Med 2018;44:1470-82.
22. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
23. McDaniel MS, Schoeb T, Swords WE. Cooperativity between Stenotrophomonas maltophilia and Pseudomonas aeruginosa during Polymicrobial Airway Infections. Infect Immun 2020;88:e00855-19.
24. Kataoka D, Fujiwara H, Kawakami T, Tanaka Y, Tanimoto A, Ikawa S, et al. The indirect pathogenicity of Stenotrophomonas maltophilia. Int J Antimicrob Agents 2003;22:601-6.
25. Adukauskiene D, Ciginskiene A, Adukauskaite A, Koulenti D, Rello J. Clinical features and outcomes of monobacterial and polybacterial episodes of ventilator-associated pneumonia due to multidrug-resistant Acinetobacter baumannii. Antibiotics (Basel) 2022;11:892.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):452-459
https://doi.org/10.4266/acc.2023.00766

| pISSN 2586-6052 | eISSN 2586-6060

Biomarkers to predict mortality in patients with Fournier's gangrene admitted to the intensive care unit after surgery in South Korea

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Background: The use of biomarkers to predict patient outcomes may be crucial for patients admitted to the intensive care unit (ICU) following surgery because biomarkers guide clinicians in tailoring treatment plans accordingly. Therefore, we aimed to identify potential biomarkers to predict the prognosis of patients with Fournier's gangrene (FG) admitted to the ICU after surgery.
Methods: We enrolled patients with FG admitted to our hospital between January 2013 and December 2022. We retrospectively analyzed patient characteristics, factors related to management, scores known to be associated with the prognosis of FG, and laboratory data.
Results: The study population included 28 survivors and 13 nonsurvivors. The initial serum lactate level taken in the emergency department; white blood cell, neutrophil, and platelet counts; delta neutrophil index and international normalized ratio; albumin, glucose, HCO_3, and postoperative lactate levels; and the laboratory risk indicator for necrotizing fasciitis differed between survivors and nonsurvivors. Postoperative lactate and initial albumin levels were independent predictors of mortality in patients with FG. The postoperative lactate level was the best indicator of mortality (area under the curve, 0.877; 95% confidence interval, 0.711–1.000). The optimal cutoff postoperative lactate level for predicting mortality was 3.0 mmol/L (sensitivity, 80.0%; specificity, 95.0%).
Conclusions: Postoperative lactate and initial albumin levels could be potential predictors of mortality in patients with FG admitted to the ICU after surgery, and the optimal cutoff postoperative lactate and initial albumin levels to predict mortality were 3.0 mmol/L and 3.05 g/dl, respectively.

Key Words: albumin; biomarkers; Fournier gangrene; intensive care unit; neutrophil

Original Article

Received: June 2, 2023
Revised: August 3, 2023
Accepted: August 30, 2023

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INTRODUCTION

Fournier's gangrene (FG) is a rare but serious bacterial infection that affects the genital and perineal regions of the body [1]. It is also known as necrotizing fasciitis of the perineum and can be life-threatening if left untreated. This condition is more common in men than in women [2], and usually occurs in people with weakened immune systems or other underlying health conditions [3]. It is often caused by bacteria such as *Escherichia coli, Klebsiella,* and *Pseudomonas aeruginosa* [4].

The symptoms of FG typically begin with pain, swelling, redness in the genital or perineal

areas, and fever. As the infection progresses, the affected tissue may become necrotic, leading to skin and muscle death and the formation of pus and gas in the affected area. If left untreated or delayed, FG can lead to various complications such as sepsis, shock, organ failure, and even death [5]. Patients with FG and critical illnesses typically require prompt and aggressive treatment, including antibiotics, surgical debridement, and intensive care management.

Although many studies have evaluated biomarkers to predict disease prognosis [3,6-8], relatively fewer studies have evaluated patients admitted to the intensive care unit (ICU) after surgery. Although patients admitted to the ICU receive medically advanced management, the mortality rate associated FG is still high. The use of biomarkers to predict patient outcomes may be particularly crucial for patients admitted to the ICU following surgery. Therefore, we conducted this study to identify possible biomarkers that can predict the prognosis of patients with FG admitted to the ICU after surgery.

KEY MESSAGES

- The use of biomarkers to predict patient outcomes may be particularly crucial for patients admitted to the intensive care unit (ICU) following surgery.
- Postoperative lactate and initial albumin levels could be potential predictors of mortality in patients with Fournier's gangrene admitted to the ICU after surgery.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (No. CR323018). Since the data were analyzed retrospectively and the identities of the patients were hidden, the requirement for informed consent was waived.

Patient Selection

A total of 84 patients (age ≥18 years) with FG were admitted via the emergency department in Wonju Severance Christian Hospital between January 2013 and December 2022. Medical records and initial computed tomography scans of these patients were reviewed retrospectively. Thirty-three patients who did not undergo surgery and/or were not admitted to the ICU were excluded. Patients with isolated scrotal and perianal abscesses without necrotizing fasciitis of the perineal or inguinal areas were also excluded. Thus, after excluding a total of 43 patients, the remaining 41 patients with FG were included in this study (Figure 1).

Management of FG in Wonju Severance Christian Hospital

Surgical intervention and medical resuscitation were performed to manage the patients with FG. Medical management included initial fluid resuscitation, since patients may present with septic shock. Vasopressors may be added when patients with low blood pressure are unresponsive to fluid resuscitation. The initiation of empirical broad-spectrum antibiotic treatment while awaiting the culture sensitivity results is also important. Targeted antibiotic therapy to cover the organisms associated with FG should be initiated after obtaining the antibiotic-sensitivity results. Radical wide excision of necrotic tissue was performed as an essential element of surgical intervention for patients with FG. Irrigation and drainage were also performed. Patients with suspected significant sphincteric involvement underwent stoma formation to prevent fecal wound contamination. The stoma site was determined intraoperatively.

Definitions and Data Collection

The medical charts of the enrolled patients were retrospectively reviewed. Patient characteristics, including clinical data (age, sex, body mass index, underlying diseases, mean blood pressure, pulse rate, body temperature, septic shock at the initial presentation, surgical treatment, stoma formation, cystostomy formation), laboratory findings (initial lactate level taken in the emergency department, postoperative lactate

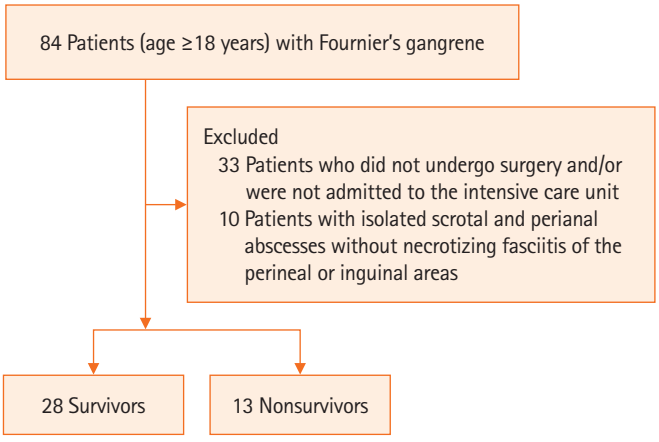

Figure 1. Flowchart of the study.

level and lactate clearance; white blood cell [WBC], neutrophil, lymphocyte, and platelet counts; delta neutrophil index [DNI] and international normalized ratio [INR]; and C-reactive protein [CRP], procalcitonin, creatinine, and albumin levels), hospital length of stay (LOS), ICU LOS, and overall mortality. The Fournier's Gangrene Severity Index (FGSI) was calculated using the formula described by Laor et al. [9]. Data for nine parameters, including body temperature, pulse rate, respiratory rate, hematocrit, leukocyte counts, and serum sodium, potassium, creatinine, and bicarbonate levels, were collected for calculation. The Uludag Fournier's Gangrene severity index (UFGSI) proposed by Yilmazlar et al. [10] was also calculated. Age and disease dissemination scores were added to the FGSI to calculate UFGSI. Scoring was performed during initial presentation at the emergency department. The total WBC count and the hemoglobin, sodium, glucose, serum creatinine, and CRP levels were used to calculate the laboratory risk indicator for necrotizing fasciitis (LRINEC) [11]. The neutrophil-to-lymphocyte ratio was calculated.

Statistical Analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range), and a comparative analysis was performed using Student t-test or the Mann-Whitney test. Categorical variables were analyzed using the chi-square test with Yates' correction for continuity and Fisher's exact test. Multivariate analysis was performed using logistic regression to identify independent risk factors. A receiver operating characteristic (ROC) curve was constructed and the Youden Index method was used to determine the optimal cutoff values for predicting mortality. Statistical analyses were performed using R statistical software (ver. 4.1.0; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$.

RESULTS

Patient Characteristics in the Survivor and Nonsurvivor Groups

There was a significant difference in the mean age observed between the survivor group and the nonsurvivor group (59.9±13.5 vs. 63.7±14.2, P=0.421). The proportion of male patients did not differ between the two groups (25 [89.3%] vs. 10 [76.9%], P=0.361). The nonsurvivor group showed significantly more patients with liver diseases (6 [10.3%] vs. 9 [33.3%], P=0.015). A significant difference was observed in the initial lactate level (2.1±1.6 vs. 7.0±4.8 mmol/L, P=0.004), postoperative lactate level (1.8±0.9 vs. 5.8±4.3 mmol/L, P=0.016), initial WBC count (16.1±9.4 vs. 9.0±6.0 $\times 10^9$/L, P=0.006), initial neutrophil count (14.5±9.0 vs. 7.9±5.5 $\times 10^9$/L, P=0.006), initial platelet count (208.9±128.7 vs. 112.2±111.3 $\times 10^9$/L, P=0.020), DNI (7.9%±10.1% vs. 27.6%±24.4%, P=0.014), albumin level (3.2±0.8 vs. 2.4±0.5 g/dl, P<0.001), INR (1.2±0.2 vs. 1.7±0.7, P=0.043), glucose level (209.9±141.0 vs. 128.3±48.0 mg/dl, P=0.009), and HCO_3 level (22.6±4.4 vs. 17.1±6.9 mmol/L, P=0.018) between the survivor and nonsurvivor groups. The nonsurvivor group demonstrated a significantly higher LRINEC score (7.5±2.8 vs. 5.7±1.5, P=0.010) compared to the survivor group. Table 1 provides a comprehensive description of all the details.

Identification of Independent Risk Factors for Predicting Mortality in Patients with FG

A logistic regression analysis was conducted to assess independent risk factors, which encompassed variables such as age, sex, body mass index, initial lactate level, postoperative lactate level, WBC count, neutrophil count, platelet count, DNI, albumin level, INR, glucose level, HCO_3 level, and LRINEC. The following risk factors were independently correlated with mortality: postoperative lactate level (odds ratio [OR], 2.87; 95% confidence interval [CI], 1.18–7.02; P=0.021), and initial albumin level (OR, 0.07; 95% CI, 0.01–0.49; P=0.007) (Table 2).

Microbial Pathogens Identified in Cases of FG

In this study, *E. coli* was the predominant organism identified among the enrolled patients (n=15, 21.1%). Additionally, other organisms such as *Klebsiella* species (18.3%), *Streptococci* (15.5%), and *Enterococci* (14.1%) were also detected (Table 3).

Optimal Cutoff Values of the Postoperative Lactate and Initial Albumin Levels

ROC curves were generated for postoperative lactate and initial albumin levels to predict mortality in patients diagnosed with FG. The area under the curve (AUC) for postoperative lactate was 0.877 (95% CI, 0.711–1.000), while for initial albumin, it was 0.827 (95% CI, 0.738–0.997). The optimal cutoff value for postoperative lactate was determined as 3.0 mmol/L, with a sensitivity of 80.0% and specificity of 95.0%. Similarly, the optimal cutoff value for initial albumin was 3.05 g/dl, with a sensitivity of 92.3% and specificity of 57.1%. Detailed results can be found in Table 4 and Figure 2.

Table 1. Patient characteristics in the survivor and nonsurvivor groups

Variable	Survivor (n=28)	Nonsurvivor (n=13)	P-value
Age (yr)	60±14	64±14	0.421
Male	25 (89.3)	10 (76.9)	0.361[a]
Body mass index (kg/m^2)	25.1±5.9	21.7±3.5	0.028
Underlying disease			
Hypertension	15 (53.6)	3 (23.1)	0.136
Diabetes mellitus	12 (42.9)	7 (53.8)	0.749
Liver disease	5 (17.9)	6 (46.2)	0.073[a]
Renal disease	4 (14.3)	1 (7.7)	0.998[a]
Pulmonary disease	0	1 (7.7)	0.317[a]
Blood pressure (mm Hg)	82.5±18.9	77.1±16.9	0.366
Pulse rate	101.6±23.0	111.8±26.1	0.239
Body temperature (°C)	37.5±0.9	37.2±1.2	0.379
Septic shock at the initial presentation	5 (17.9)	3 (23.1)	0.692
Stoma formation	15 (53.6)	7 (53.8)	0.999
Cystostomy	2 (7.1)	0	0.999[a]
Laboratory finding			
Initial lactate (mmol/L)	2.1±1.6	7.0±4.8	0.004
Postoperative lactate (mmol/L)	1.8±0.9	5.8±4.3	0.016
Lactate clearance	0.5±1.6	2.0±3.2	0.168
Initial WBC count (×10^9/L)	16.1±9.4	9.0±6.0	0.006
Initial neutrophil count (×10^9/L)	14.5±9.0	7.9±5.5	0.006
Initial lymphocyte count (×10^9/L)	0.7±0.4	0.5±0.2	0.067
Initial hemoglobin (g/dl)	11.7±2.2	10.9±2.6	0.367
Initial platelet count (×10^9/L)	208.9±128.7	112.2±111.3	0.020
Initial DNI (%)	7.9±10.1	27.6±24.4	0.014
Initial CRP level (mg/dl)	21.7±9.6	20.0±16.4	0.731
Initial PCT level (ng/ml)	5.4±7.0	13.8±12.8	0.119
Initial albumin level (g/dl)	3.2±0.8	2.4±0.5	<0.001
Initial INR	1.2±0.2	1.7±0.7	0.043
Initial creatinine level (mg/dl)	2.1±2.1	2.6±2.0	0.439
Initial glucose level (mg/dl)	209.9±141.0	128.3±48.0	0.009
Initial HCO_3 level (mmol/L)	22.6±4.4	17.1±6.9	0.018
FGSI	7.0±3.6	8.6±5.0	0.301
UFGSI	9.7±3.7	11.9±6.2	0.250
LRINEC	5.7±1.5	7.5±2.8	0.010
Neutrophil-lymphocyte ratio	24.5±19.0	16.5±14.0	0.142
Hospital length of stay (day)	55.9±52.0	37.2±43.2	0.240
ICU length of stay (day)	5.0±4.2	22.5±40.7	0.149

Values are presented as mean±standard deviation or number (%).
WBC: white blood cell; DNI: delta neutrophil index; CRP: C-reactive protein; PCT: procalcitonin; INR: international normalized ratio; FGSI: Fournier's gangrene severity index; UFGSI: Uludag Fournier's gangrene severity index; LRINEC: laboratory risk indicator for necrotizing fasciitis; ICU: intensive care unit.
a) Fisher's exact test.

DISCUSSION

Our results showed that the postoperative lactate and preoperative albumin levels were major predictors in ICU patients with FG. The optimal cutoff values for serum postoperative lactate and initial albumin levels were 3.0 mmol/L (sensitivity, 80.0%; specificity, 95.0%) and 3.05 g/dl (sensitivity, 92.3%; specificity, 57.1%), respectively.

Table 2. Multivariate analysis using a logistic regression model to predict mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Male	2.50 (0.43–14.54)	0.308		
Initial lactate (mmol/L)	1.71 (1.16–2.54)	0.007		
Initial WBC count ($\times 10^9$/L)	1.00 (1.00–1.00)	0.027		
Initial neutrophil count ($\times 10^9$/L)	1.00 (1.00–1.00)	0.028		
Initial platelet count ($\times 10^9$/L)	0.99 (0.99–1.00)	0.034		
Initial DNI (%)	1.07 (1.02–1.12)	0.007		
Initial INR	31.02 (1.54–622.99)	0.025		
Initial glucose level (mg/dl)	0.99 (0.98–1.00)	0.083		
Initial HCO_3 level (mmol/L)	0.83 (0.71–0.96)	0.012		
Age (yr)	1.02 (0.97–1.08)	0.401	0.99 (0.92–1.07)	0.856
Postoperative lactate (mmol/L)	2.87 (1.18–7.02)	0.021	2.87 (1.18–7.02)	0.021
Initial albumin level (g/dl)	0.09 (0.02–0.48)	0.005	0.07 (0.01–0.49)	0.007
LRINEC	1.41 (1.01–2.00)	0.044	1.47 (0.97–2.22)	0.066

HR: hazard ratio; CI: confidence interval; WBC: white blood cell; DNI: delta neutrophil index; INR: international normalized ratio; LRINEC: laboratory risk indicator for necrotizing fasciitis.

Table 3. Causative bacterial organisms for Fournier's gangrene

Bacterial organism	Total (n=71)
Escherichia coli	15 (21.1)
Klebsiella species	13 (18.3)
Streptococci	11 (15.5)
Enterococci	10 (14.1)
Staphylococci	10 (14.1)
Acinetobacter species	3 (4.2)
Pseudomonas	2 (2.8)
Candida species	2 (2.8)
Gram positive rods	1 (1.4)
Others	4 (5.6)

Values are presented as number (%).

Table 4. Characteristics of postoperative lactate and initial albumin levels

Variable	Optimal cutoff value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Postoperative lactate (mmol/L)	3.00	80.0	95.0	0.877 (0.711–1.000)
Initial albumin (g/dl)	3.05	92.3	57.1	0.827 (0.738–0.997)

AUC: area under the curve; CI: confidence interval.

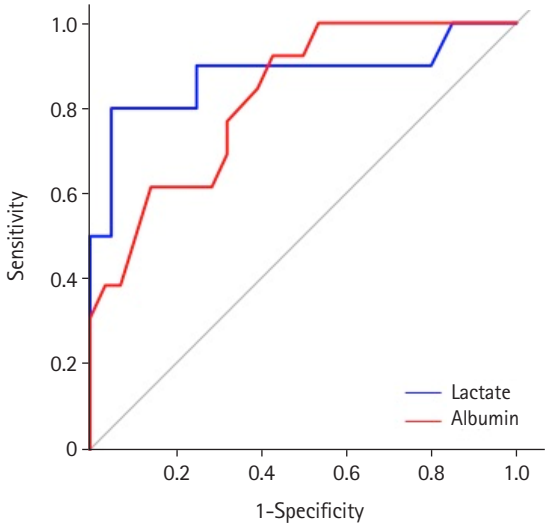

Figure 2. Receiver operating characteristics curves for the lactate level and the albumin level between the survivors and nonsurvivors.

The serum lactate level is a widely utilized biomarker in critically ill patients that indicates the degree of tissue hypoxia and anaerobic metabolism [12]. Under conditions such as sepsis, shock, and respiratory failure, inadequate oxygen supply to tissues triggers anaerobic metabolism, resulting in lactate accumulation in the bloodstream [13]. Significant differences were observed in the initial lactate levels between survivors and nonsurvivors during the univariate analysis, but not in the multivariate analysis. In contrast, the postoperative lactate levels can be influenced by resuscitation after initial evaluation and surgical excision. Therefore, the postoperative lactate level may be a more accurate biomarker to predict mortality than the initial lactate level because the postoper-

ative lactate level reflects the patient's condition after initial treatment.

Although the AUC of the serum albumin level was lower than that of the postoperative lactate level, the serum albumin level emerged as an independent predictor of mortality in patients diagnosed with FG. Hypoalbuminemia can occur in critically ill patients and is influenced by various factors, including physiological responses triggered by infection [14]. Serum albumin levels can be affected by changes in albumin synthesis and catabolism as well as increased endothelial permeability leading to albumin loss into the extravascular space [14]. The latter mechanism seems to play a substantial role in hypoalbuminemia observed in patients with metabolic stress, leading to the redistribution of albumin from the intravascular to the interstitial compartment. Additionally, serum albumin levels can reflect a patient's nutritional status and immune function [15]. Therefore, hypoalbuminemia may contribute to disease progression and, conversely, a worsened disease course may further reduce serum albumin levels. A previous study indicated that hypoalbuminemia could serve as a predictive factor for mortality in patients diagnosed with FG [16].

In this study, despite the significant difference observed in LRINEC scores between survivors and nonsurvivors during the univariate analysis and its inclusion in the regression model, LRINEC was not identified as an independent predictor of mortality. Wong et al. [11], who constructed the LRINEC, demonstrated that it is considered a robust scoring system that can effectively identify even clinically early cases of necrotizing fasciitis. The LRINEC includes six laboratory markers that are important for critically ill patients. However, the patients enrolled to construct this scoring system may be not systemically ill patients with severe necrotizing fasciitis. Insufficient information was available to understand the patient's condition. Because our study was based on critically ill patients admitted to the ICU, the LRINEC may not be accurate for predicting mortality. Previous studies have identified other scores for FG, such as the FGSI and the UFGSI, as possible predictive markers of poor outcomes [4,17-20]. However, in this study, FGSI and UFGSI scores did not differ between survivors and nonsurvivors. The observed differences in results between our study and previous studies are likely influenced by the combination of low FG prevalence, small sample sizes in both our study and previous studies, and the specific patient selection criteria focusing on ICU-admitted patients in our research. Data from 80 patients were used to construct the UFGSI, but mortality occurred in only 17 patients. In addition, only 21 of these 80 patients were admitted to the ICU [18]. Therefore, the UFGSI may show limited ability to predict outcomes in critically ill patients.

The DNI is a laboratory parameter that examines leukocyte differentials by utilizing two independent channels, namely the myeloperoxidase channel and the lobularity/nuclear density channel [21]. The DNI is derived by quantifying the variance between leukocyte differentials measured in the myeloperoxidase and lobularity/nuclear density channels, providing an indication of the proportion of immature granulocytes present in the bloodstream [21]. Numerous studies have demonstrated that the DNI can serve as a valuable biomarker in predicting disease severity and prognosis in patients with diverse infectious conditions or sepsis [3,22,23]. However, the DNI was not an independent predictor in this study, although it was significantly higher in nonsurvivors in the univariate analysis. In this study, because the target patient group was analyzed only for patients admitted to an ICU, we assumed that the difference in DNI between patients was not significant.

Several limitations need to be considered in this study. Firstly, there was a possibility of selection bias due to its retrospective nature. Secondly, the sample size was relatively small since only patients from a single center were included, which may have affected the representativeness of the enrolled patients. Thirdly, potential variations in the timing and approaches to patient management might have been present due to the involvement of different physicians treating the enrolled patients throughout the study period. Lastly, as the analysis encompassed patient data collected over an extended duration, certain confounding factors, such as advancements in ICU care over time, may not have been adequately addressed.

In conclusion, the postoperative lactate and initial albumin levels could be potential predictors of mortality in patients with FG who were admitted to the ICU after surgery, and the optimal cutoff postoperative lactate and initial albumin levels to predict mortality were 3.0 mmol/L and 3.05 g/dl, respectively. To validate our findings, it is essential to conduct large-scale multicenter prospective studies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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Conceptualization: ISS. Data curation: ISS. Formal analysis: KK. Methodology: ISS, SA, SCG. Project administration: ISS. Visualization: SA, SCG. Writing – original draft: ISS. Writing – review & editing: ISS, KK.

REFERENCES

1. Carroll PR, Cattolica EV, Turzan CW, McAninch JW. Necrotizing soft-tissue infections of the perineum and genitalia. Etiology and early reconstruction. West J Med 1986;144:174-8.
2. Orhan E, Şenen D. Using negative pressure therapy for improving skin graft taking on genital area defects following Fournier gangrene. Turk J Urol 2017;43:366-70.
3. Shin IS, Gong SC, An S, Kim K. Delta neutrophil index as a prognostic factor for mortality in patients with Fournier's gangrene. Int J Urol 2022;29:1287-93.
4. Garg G, Singh V, Sinha RJ, Sharma A, Pandey S, Aggarwal A. Outcomes of patients with Fournier's Gangrene: 12-year experience from a tertiary care referral center. Turk J Urol 2019;45:S111-6.
5. Gadler T, Huey S, Hunt K. Recognizing Fournier's gangrene in the emergency department. Adv Emerg Nurs J 2019;41:33-8.
6. Kim KM, Seong SH, Won DY, Ryu H, Kim IY. The prognostic factors and severity index in Fournier's gangrene. J Korean Soc Coloproctol 2010;26:29-33.
7. Eray IC, Dalci K, Gumus S, Yalav O, Saritas AG, Boz A, et al. The role of C-reactive protein ratio in predicting mortality in patients with Fournier gangrene. Ann Coloproctol 2023;39:223-30.
8. Friederichs J, Hutter M, Hierholzer C, Novotny A, Friess H, Bühren V, et al. Procalcitonin ratio as a predictor of successful surgical treatment of severe necrotizing soft tissue infections. Am J Surg 2013;206:368-73.
9. Laor E, Palmer LS, Tolia BM, Reid RE, Winter HI. Outcome prediction in patients with Fournier's gangrene. J Urol 1995;154:89-92.
10. Yilmazlar T, Ozturk E, Ozguc H, Ercan I, Vuruskan H, Oktay B. Fournier's gangrene: an analysis of 80 patients and a novel scoring system. Tech Coloproctol 2010;14:217-23.
11. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32:1535-41.
12. Kushimoto S, Akaishi S, Sato T, Nomura R, Fujita M, Kudo D, et al. Lactate, a useful marker for disease mortality and severity but an unreliable marker of tissue hypoxia/hypoperfusion in critically ill patients. Acute Med Surg 2016;3:293-7.
13. Li X, Yang Y, Zhang B, Lin X, Fu X, An Y, et al. Lactate metabolism in human health and disease. Signal Transduct Target Ther 2022;7:305.
14. Wiedermann CJ. Hypoalbuminemia as surrogate and culprit of infections. Int J Mol Sci 2021;22:4496.
15. Moon JJ, Kim Y, Kim DK, Joo KW, Kim YS, Han SS. Association of hypoalbuminemia with short-term and long-term mortality in patients undergoing continuous renal replacement therapy. Kidney Res Clin Pract 2020;39:47-53.
16. Tuncel A, Aydin O, Tekdogan U, Nalcacioglu V, Capar Y, Atan A. Fournier's gangrene: three years of experience with 20 patients and validity of the Fournier's Gangrene Severity Index Score. Eur Urol 2006;50:838-43.
17. Sabzi Sarvestani A, Zamiri M, Sabouri M. Prognostic factors for Fournier's gangrene: a 10-year experience in Southeastern Iran. Bull Emerg Trauma 2013;1:116-22.
18. Üreyen O, Acar A, Gökçelli U, Atahan MK, İlhan E. Usefulness of FGSI and UFGSI scoring systems for predicting mortality in patients with Fournier's gangrene: a multicenter study. Ulus Travma Acil Cerrahi Derg 2017;23:389-94.
19. Hong KS, Yi HJ, Lee RA, Kim KH, Chung SS. Prognostic factors and treatment outcomes for patients with Fournier's gangrene: a retrospective study. Int Wound J 2017;14:1352-8.
20. Noegroho BS, Siregar S, Mustafa A, Rivaldi MA. Validation of FGSI scores in predicting Fournier gangrene in tertiary hospital. Res Rep Urol 2021;13:341-6.
21. Nahm CH, Choi JW, Lee J. Delta neutrophil index in automated immature granulocyte counts for assessing disease severity of

patients with sepsis. Ann Clin Lab Sci 2008;38:241-6.
22. Kim JW, Park JH, Kim DJ, Choi WH, Cheong JC, Kim JY. The delta neutrophil index is a prognostic factor for postoperative mortality in patients with sepsis caused by peritonitis. PLoS One 2017;12:e0182325.
23. Kong T, Park YS, Lee HS, Kim S, Lee JW, You JS, et al. The delta neutrophil index predicts the development of in-hospital hypotension in initially stable patients with pyogenic liver abscess. Sci Rep 2019;9:12105.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):460-468
https://doi.org/10.4266/acc.2022.01501

| pISSN 2586-6052 | eISSN 2586-6060

Effect of fourth hourly oropharyngeal suctioning on ventilator-associated events in patients requiring mechanical ventilation in intensive care units of a tertiary care center in South India: a randomized controlled trial

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Background: Mechanical ventilation (MV) is a necessary life-saving measure for critically ill patients. Ventilator-associated events (VAEs) are potentially avoidable complications associated with MV that can double the rate of death. Oral care and oropharyngeal suctioning, although neglected procedures, play a vital role in the prevention of VAE.

Methods: A randomized controlled trial was conducted in the intensive care units to compare the effect of fourth hourly oropharyngeal suctioning with the standard oral care protocol on VAE among patients on MV. One hundred twenty mechanically ventilated patients who were freshly intubated and expected to be on ventilator support for the next 72 hours were randomly allocated to the control or intervention groups. The intervention was fourth hourly oropharyngeal suctioning along with the standard oral care procedure. The control group received standard oral care (i.e., thrice a day) and on-demand oral suctioning. On the 3rd and 7th days following the intervention, endotracheal aspirates were sent to rule out ventilator-associated pneumonia.

Results: Both groups were homogenous at baseline with respect to their clinical characteristics. The intervention group had fewer VAEs (56.7%) than the control group (78.3%) which was significant at P<0.01. A significant reduction in the status of "positive culture" on ET aspirate also been observed following the 3rd day of the intervention (P<0.001).

Conclusions: One of the most basic preventive strategies is providing oral care. Oropharyngeal suctioning is also an important component of oral care that prevents microaspiration. Hence, fourth-hourly oropharyngeal suctioning with standard oral care significantly reduces the incidence of VAE.

Key Words: critical illness; incidence; intensive care units; mechanical ventilators; randomized controlled trials; ventilator-associated pneumonia

Original Article

Received: December 1, 2022
Revised: March 27, 2023
Accepted: August 3, 2023

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INTRODUCTION

Mechanical ventilation (MV) is a necessary life-saving measure for critically ill patients. However, it is associated with considerable, yet preventable complications. MV is not a curative intervention; however, it supports the patient until he/she recovers the ability to breathe independently. Intubation with an endotracheal tube (ETT) keeps the glottis open, leaving only the inflated cuff to protect against aspiration of contaminated oral secretions and gastric contents into the lungs [1]. Therefore, MV predisposes the patient to an increased risk of ventilator-associated events (VAEs) due to aspiration, resulting in more complications and poor outcomes.

Among all potential complications of MV, ventilator-associated pneumonia (VAP) is considered the leading cause of mortality and is a potentially preventable iatrogenic illness. However, most of the diagnostic criteria for VAP are not objective or specific. In addition, VAP surveillance has limited accuracy. Hence, the Centers for Disease Control (CDC) developed a new surveillance definition of the VAE algorithm in January 2013 based on objective, streamlined, and potentially automatable criteria that identify a broad range of conditions and complications occurring in mechanically-ventilated adult patients [2,3].

There are three definition tiers within the VAE algorithm including ventilator-associated conditions (VACs), infection-related VAC (IVAC), and possible VAP (PVAP) [2]. However, the algorithm is not meant for clinical use in the management of mechanically ventilated patients. Instead, it was created as a surveillance system to improve the reliability of detecting VAP and other mechanical ventilator-associated complications quickly and easily [4]. A VAC is the first level among the three tiers. A VAC is defined by worsening respiratory status including hypoxemia based on an increase in daily minimum FiO_2 ≥0.20 or positive end-expiratory pressure (PEEP) ≥3 cm H_2O sustained for at least 2 calendar days following a baseline period (2 calendar days) of stability or improvement. An IVAC requires the VAC criteria, followed by an abnormal leukocyte count (≥12,000/≤4,000 cells/mm^3) or temperature (>38 °C/<36 °C) along with treatment with any new antimicrobial agent. Further progression to the third level leads to probable or possible VAP, which is suggested by the presence of a pulmonary source of infection [5,6].

The use of comprehensive oral care protocols can significantly reduce VAP rates [6]. In 2001, Bergmans et al. [7] provided evidence that the key to preventing VAP is the prevention of bacterial colonization of the oropharynx. Therefore, the removal of the colonized accumulations from the oropharynx can prevent the development of VAP-related complications.

The development of VAEs can lead to a significant increase in ventilator days, hospital stays, days of antibiotics, and higher hospital morbidity and mortality compared to those of patients without VAEs [8,9]. Proper airway care is crucial to minimize the devastating side effects of an artificial airway and prevent VAE development. Therefore, the current study aims to assess the effectiveness of fourth hourly oropharyngeal suctioning with standard oral care on VAE development.

KEY MESSAGES

- Oropharyngeal suctioning is an important component of the oral care protocol that can reduce the development of ventilator-associated events by preventing microaspiration.
- Fourth hourly oropharyngeal suctioning along with standard oral care was effective and is recommended to reduce the development of ventilator-associated events.

MATERIALS AND METHODS

A randomized controlled trial design was adopted for the study. Data were collected from seven intensive care units (ICU) at a tertiary care hospital in the public health sector of South India for a period of 8 months (January-August 2022).

Sampling and Randomization

The participants were selected using a convenience sampling technique. We anticipated a 20% reduction of VAP among patients undergoing oropharyngeal suctioning compared to the control group. With 80% power and a 5% level of significance, the sample size of 54 participants in each group was estimated using a comparison of two independent proportions. After considering a 10% attrition rate, a total of 120 participants were enrolled [10]. Adult patients who were ≥18 years, expected to be mechanically ventilated for at least the next 72 hours, on enteral feeding (nasogastric or orogastric tube feeding), and receiving an H_2 receptor blocker/proton pump inhibitors were enrolled within 24 hours of intubation. Patients who were intubated for aspiration pneumonitis, reintubated, contraindicated for oral care, facial/oral surgeries, or who were receiving total parenteral nutrition were excluded from the study.

Stratified block randomization was used using the strata of sex (male, female) and Acute Physiology and Chronic Health Evaluation (APACHE) II score (≤25, >25). A random allocation sequence was generated by a statistician outside of the research team. Allocation concealment was performed using sequentially numbered opaque sealed envelopes (consort diagram) (Figure 1).

Ethical Considerations

Permission was obtained for the current study from the Institute Nursing Research Monitoring Committee (CON/NRMC/ M.Sc./2020/MSN/3) and the Institute Ethics Committee for human studies (CON/IEC/M.Sc./2020/MSN/3). The study was registered under Clinical Trial Registry India (CTRI/2022/01/039460). The procedures were performed in accordance with the ethical standards of the institution, as well as the Declaration of Helsinki (revised in 2013). After a brief explanation to the Legally authorized representative (LAR) of each enrolled patient regarding the study, informed consent was obtained from the LAR (as the patients were unable to give consent because of their critical condition and inability/unconsciousness). Patient data were stored confidentially. Confidentiality, the anonymity of the subjects, and the right to withdraw from the study were explained to the LAR before data collection.

Intervention and Data Collection

Before the intervention, the patient's vital signs were assessed,

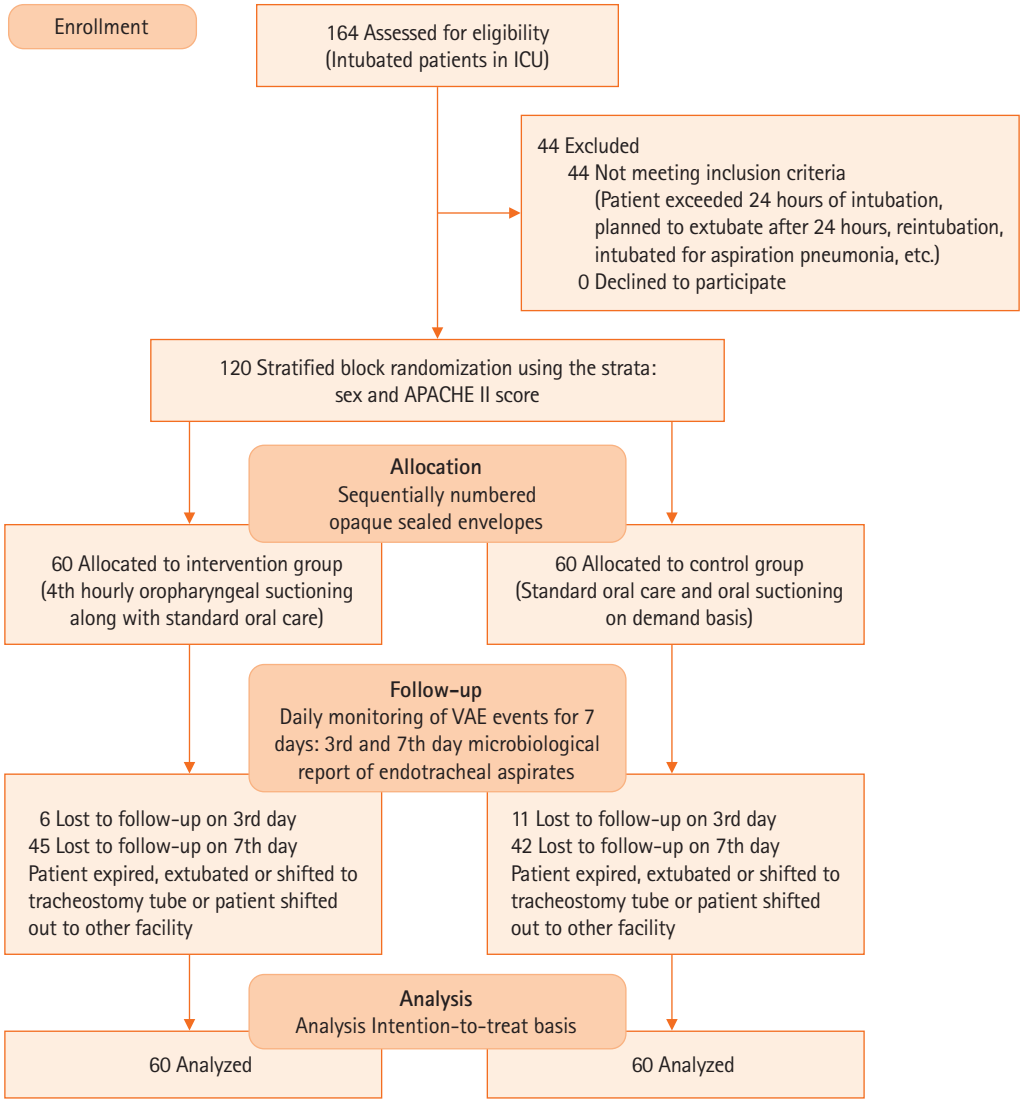

Figure 1. Consort diagram. ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; VAE: ventilator-associated event.

including oxygen saturation, respiratory rate, and pulse rate. The ventilator parameters and oxygenation were also recorded. The patient was placed in the lateral position, and under a strict aseptic technique, a suction catheter was advanced through the mouth towards the trachea approximately 3–4 inches. Suction was then applied for a maximum of up to 10–15 seconds with a suction pressure of 100–120 mm Hg. A break of 30 seconds to 1 minute was provided before the next insertion. This procedure was repeated every fourth hour, along with oral care using chlorhexidine solution, for 7 days after enrollment, or until the patient got extubated or transferred to another setting. In contrast, the participants in the control group received oral suctioning when it was required and standard oral care (oral care with chlorhexidine thrice a day). Both groups received endotracheal suctioning every hour and when required as per unit protocol.

Each participant was classified as VAE-positive or -negative using the CDC algorithm [3]. The daily minimum FiO_2 and PEEP were recorded after a period of sustainability for two days. Any value increase indicates worsening oxygenation, which reflects VAC. An IVAC was defined by a temperature >38 °C/<36 °C with or without a WBC count ≥12,000/≤4,000 cells/mm^3 and a newly started antimicrobial agent with or without worsening of oxygenation. On day 3 and day 7, tracheal specimens were collected into sterile mucus traps from both groups following standard protocol in order to isolate any microorganisms or rule out VAP. Many participants were lost to follow-up because of extubation, placement of a tracheostomy, transfer out of the ICU, leaving against medical advice, or death. The day when VAC/IVAC/PVAP criteria were met was considered the time of VAE development. Throughout the trial, the investigator continuously ensured that the ETT cuff pressure was maintained between 25 and 30 mm Hg, and the head of the bed was elevated to 30°. Detection bias was avoided because the outcome assessment was performed by another investigator who was blinded to the study group.

Data Analysis

All statistical analyses were done using SPSS ver. 25.0 (IBM Corp.) on an intention-to-treat basis to reduce attrition bias. The categorical variables (such as sex, education, type of ETT, the incidence of VAE, etc.) were expressed as frequencies and percentages. The continuous data (such as age, body mass index, ETT cuff pressure, duration of intubation, etc.) were expressed as means with standard deviations, or medians with interquartile ranges. Comparison of the baseline characteristics between the groups was done using the chi-square test, Fisher's exact test, Mann-Whitney U-test, and independent Student t-test. The number of VAE-positive participants was compared between the groups using the chi-square test or Fisher's exact test. Kaplan-Meier survival analysis was performed to determine the time to VAE. Differences between the survival curves across each group were tested for significance by the log-rank statistic.

RESULTS

The study gathered data from a total of 120 participants from seven ICUs. The groups were homogeneous with regard to religion, nativity, occupation, and education. The mean ages in the intervention and control groups were 50.75 years and 48.85 years, respectively. In terms of sex, both groups had male preponderance. The majority of the participants were intubated with a size 7.5 ETT in both groups. The groups were similar with regard to the duration of intubation before enrollment (P=0.224), their APACHE II score (P=0.148), type of intubation (P=0.273), and type of suction (P=1.000) (Table 1).

There was a significant difference in positive microbiological culture reports between the intervention group (48.3%) and control group (71.7%) following the 3rd day of the intervention (P<0.001). However, only a few participants (intervention, 9; control, 7) reached day 7, as most of them were either extubated, transitioned to a tracheostomy, transferred out to another setting or died (Table 2). The total duration of MV (in hours) was 83.5 (60.0–145.3) in the intervention group and 78.5 (59.3–139.0) in the control group, which was statistically non-significant. The number of days in the ICU was 9 (5.25–14.0) in the intervention group, and 7 (4.25–12.75) in the control group.

Fewer participants (56.70%) developed VAE in the intervention group than did in the control group (78.30%) (P=0.011). There were also fewer PVAP incidences in the intervention group (51.67%) than in the control group (71.67%), although the difference was not statistically significant (P=0.06). There was no statistically significant difference observed between VAC and IVAC. Although there was a trend for lower VAC cases in the intervention group as compared to in the control group, the number of IVAC events was similar in both groups (Table 3). There was no association between VAE and some of the selected clinical variables such as temperature, APACHE II score, random blood sugar, type of suction, type of intubation, etc. (Table 4).

The characterizations of the participants' survival times are

Table 1. Comparison of intubation and ventilation-related parameters between intervention and control groups (N=120)

Variable	Intervention (n=60)	Control (n=60)	P-value
Size of ETT (mm)			0.522[a]
6.5	0	1 (1.7)	
7	7 (11.7)	7 (11.7)	
7.5	33 (55.0)	28 (46.7)	
8	20 (33.3)	24 (40.0)	
Duration of hospital stay (day)	3.0 (2.0–4.8)	3.0 (2.0–4.0)	0.593[b]
Daily minimum FiO_2 (%)	40.0 (40.0–57.5)	40.0 (40.0–60.0)	0.827[b]
Daily minimum PEEP (cm H_2O)	5.0 (5.0–6.0)	5.0 (5.0–5.0)	0.254[b]
Type of intubation			0.273[c]
Emergency	28 (46.7)	34 (56.7)	
Elective	32 (53.3)	26 (43.3)	
Type of suction			1.000[c]
Open	36 (60.0)	36 (60.0)	
Closed	24 (40.0)	24 (40.0)	
DOI (before enrollment) (hr)	12.8±6.4	14.2±6.5	0.224[d]
APACHE II score[d]	16.0±6.1	16.8±6.9	0.500[d]

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
ETT: endotracheal tube; FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; DOI: duration of intubation; APACHE: Acute Physiology and Chronic Health Evaluation.
a) Fisher's exact test; b) Mann-Whitney U-test; c) Chi-square test; d) Independent Student t-test.

Table 2. Microbiology profiles by day and group (N=120)

Microbiology report	Intervention	Control	P-value
Day 3			<0.001[a]
Culture positive	29 (48.3)	43 (71.7)	
Culture negative	25 (41.7)	6 (10.0)	
Day 7			0.666[b]
Culture positive	8 (13.3)	5 (8.3)	
Culture negative	1 (1.7)	2 (3.3)	

Values are presented as number (%).
a) Chi-square test; b) Fisher's exact test.

Table 3. Comparison of ventilator-associated events (N=120)

Event	Intervention	Control	P-value
Ventilator-associated condition			0.114[a]
Yes	1 (1.7)	6 (10.0)	
No	59 (98.3)	54 (90.0)	
Infection-related ventilator-associated condition			1.000[b]
Yes	9 (15.0)	9 (15.0)	
No	51 (85.0)	51 (85.0)	
Possible ventilator-associated pneumonia			0.069[b]
Yes	31 (51.7)	43 (71.7)	
No	29 (48.3)	17 (28.3)	
Ventilator-associated event			0.011[b]
Yes	34 (56.7)	47 (78.3)	
No	26 (43.3)	13 (21.7)	

Values are presented as number (%).
a) Fisher's exact test; b) Chi-square test.

shown in Table 5 and Figure 2. The median time to VAE was 4 days (95% confidence interval [CI,] 3.780–4.220 days) in the intervention group and 4 days (95% CI, 3.677–4.323 days) in the control group. The Kaplan-Meier survival curves and log-rank test analysis also revealed no significant difference in the time to VAE (in days) based on the intervention.

DISCUSSION

Aspiration of oral secretions one of the most common causes of pneumonia in mechanically ventilated patients [11]. In patients with oral ETT intubation, approximately 7.5 ml of secretions can accumulate in the oropharynx in 4 hours [1], which can be microaspirated. Therefore, removal of these secretions is necessary to prevent aspiration. The oral cavity is also an important source of bacteria; the ETT can act as a conduit from the oral cavity to the lung by which bacteria travel and cause VAP. Therefore, providing oral care to patients on MV can significantly reduce the relative risk of VAP development

Table 4. Association between ventilator-associated events and selected clinical parameters (N=120)

Parameter	Ventilator-associated event		P-value
	Present	Absent	
Type of intubation			0.446[a]
Emergency	41 (66.1)	21 (33.9)	
Elective	40 (69.0)	18 (31.0)	
Type of suction			0.359[a]
Open	50 (69.4)	22 (30.6)	
Closed	31 (64.6)	17 (35.4)	
Duration of intubation before enrollment (hr)	13.96±6.05	12.49±7.15	0.241[b]
Duration of hospital stay (day)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.610[c]
Daily minimum FiO_2 (%)	40.0 (40.0–60.0)	40.0 (40.0–60.0)	0.995[c]
Daily minimum positive end-expiratory pressure (cm H_2O)	5.0 (5.0–5.50)	5.0 (5.0–5.0)	0.765[c]
APACHE II score	16.0 (12.0–21.0)	16.0 (11.0–21.0)	0.770[c]
Body temperature (°C)	36.7 (36.7–37.2)	36.7 (36.7–37.2)	0.456[c]
Respiratory rate (/min)	21.0 (18.0–27.0)	20.0 (15.0–27.0)	0.560[c]
Random blood sugar (mg/dl)	142.0 (111.5–206.5)	152.0 (109.0–191.0)	0.860[c]
White blood cell (/mm^3)	15.0 (10.0–19.0)	16.0 (12.0–21.0)	0.257[c]

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
APACHE: Acute Physiology and Chronic Health Evaluation.
a) Chi-square; b) Independent Student t-test; c) Mann-Whitney U-test.

Table 5. Survival time (time to ventilator-associated events) of participants (N=120)

	Day to ventilator-associated events				P-value[a]
	Median estimate	Standard error	95% Confidence interval		
			Lower	Upper	
Intervention	4	0.112	3.780	4.220	0.770
Control	4	0.165	3.677	4.323	

a) Mantel-Cox log-rank test.

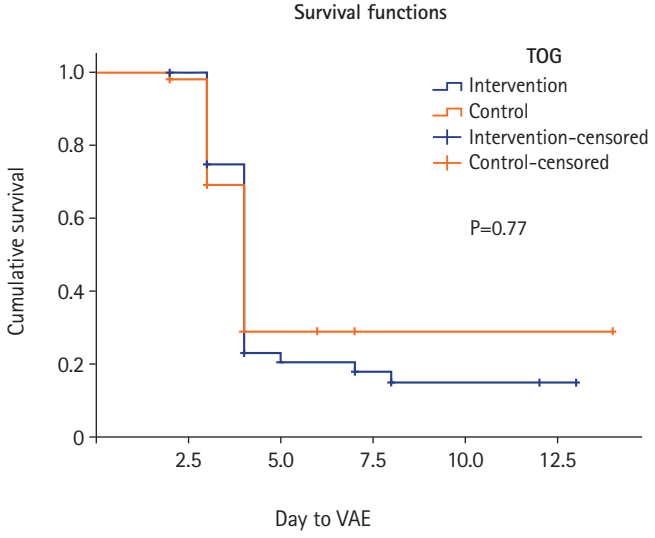

Figure 2. Kaplan-Meier survival curve. TOG: type of group; VAE: ventilator-associated event.

[12]. Despite its importance, oral care is commonly neglected in mechanically ventilated patients. Therefore, practicing an evidence-based oral care program can improve oral health, reduce the incidence of VAP statistically [10], and thereby lower the incidence of VAE.

One promising study which implemented the deep oropharyngeal suctioning to reduce oropharyngeal secretion pooling as the intervention (along with routine oral care with chlorhexidine), has identified decreased and incidence of aspiration and VAE [13]. Similarly, the current study also found that implementing fourth hourly oropharyngeal suctioning along with standard oral care reduces the incidence of development of VAE in the intervention group. The findings were consistent with the study conducted by Garcia et al. [6], who reported that suctioning every sixth hour along with other oral care measures can reduce the rate of VAP. In contrast to the pres-

ent study findings, Atashi et al. [14] showed that deep mouth and throat suctioning every 4th, 6th, 8th, 12th hour along with other measures (depending upon the oral condition) did not decrease the incidence of VAP.

The CDC endorsed a new surveillance strategy based on VAE to assess complications in patients receiving MV. The VAE surveillance shifts the focus away from infectious etiologies like VAP toward other common complications related to a ventilator [3]. However, in this study, VAE surveillance corresponds to VAP surveillance because the data matched with the VAP rates assessed by the hospital infection control committee.

The APACHE II is a score that estimates the severity of disease and mortality of ICU patients. Studies show that the risk of developing VAP increases with an increase in the APACHE II score [15]. In contrast, our study and that of Nakahashi et al. [16] found that the APACHE II score had no association with the VAE and no-VAE groups. Previous studies have shown that the closed type of suctioning is associated with a lower risk of VAP development than is open suction [17,18]. In contrast, Hamishekar et al. [19] did not find significant differences in VAP development using closed or open suctioning. Similarly, the current study also did not find any difference in VAE events among the open and closed suctioning groups.

Oral care interventions such as oropharyngeal suctioning are performed by nurses to reduce ventilator complications. Many studies have been conducted to evaluate the relationship between oral care interventions and the prevention of VAP. However, few studies have evaluated the relationship between oral care interventions and VAE using the new surveillance protocol. VAE and VAP are two separate but related conditions; therefore, reducing VAP will ultimately minimize the incidence of VAE. A study assessing the effect of 4th hourly oropharyngeal aspiration on the incidence of VAP revealed a significant difference in VAP incidence in the intervention (14.89%) and control (39.58%) groups [20]. However, a surveillance study illustrates that oral care with chlorhexidine can lower the VAP rates, but is unlikely to minimize VAE [21]. In contrast with this, the current study reported a significant effect of 4th hourly oropharyngeal suctioning on VAE incidence, and a lower incidence of VAC and PVAP in the intervention group. The positivity of microbiological cultures from endotracheal aspiration on the 3rd day was significantly higher in the control group than it was in the intervention group (P<0.001). However, a similar study did not find a significant difference in the microbiology reports after the 3rd or 5th day of their intervention [14]. Yet Gershonovitch et al. [22] described that after oropharyngeal suctioning, oral care with 0.12% chlorhexidine, a thorough toothbrushing, and cleansing of the oral cavity, there were fewer cases of VAP in the intervention group (16.19%) than in the control group (25.9%) (P=0.084).

VAE are closely related to patient outcomes, such as the length of hospital stay, number of ventilator-free days, and mortality [23,24]. However, we found no significant difference in the length of ICU stay or MV duration between the groups. Moreover, the duration of MV and ICU stay in the intervention group was minimally longer than that of the control group.

This finding might have been attributed to mortality events in both the groups and patients leaving against medical advice. Survival analysis also shows no difference in the time to the VAE between the groups. These findings may also be due to a lack of representation in terms of sample size, and loss to follow-up until the completion of the intervention period.

The limitations of the study include its smaller sample size, and performance at a single tertiary care center. Patient follow-up for mortality was not performed. Therefore, a large-scale multi-center study with long-term health outcomes may also be conducted for better generalization of the study findings for the proposed intervention.

VAE are the most common complications of MV. A patient's normal defense mechanisms are compromised during mechanically ventilation, making the patient prone to complications related to ventilation itself. One of the most basic preventive strategies against these complications is to provide oral care and oropharyngeal suctioning in particular. We found that 4th hourly oropharyngeal suctioning along with standard oral care can be effectively reduce VAE.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Methodology: all authors. Formal analysis: all authors. Data curation: KB, LR, MS, RM, HTL. Visualization: KB, LR, MS, HTL, RS. Project administration: LR. Writing–original draft: KB, LR, HTL. Writing–review & editing: all authors.

REFERENCES

1. Sole ML, Penoyer DA, Bennett M, Bertrand J, Talbert S. Oropharyngeal secretion volume in intubated patients: the importance of oral suctioning. Am J Crit Care 2011;20:e141-5.
2. Burja S, Belec T, Bizjak N, Mori J, Markota A, Sinkovič A. Efficacy of a bundle appr oach in preventing the incidence of ventilator associated pneumonia (VAP). Bosn J Basic Med Sci 2018;18:105-9.
3. United States Department of Health and Human Services, Centers for Disease Control and Prevention. Ventilator-associated event (VAE). Centers for Disease Control and Prevention; 2019 [cited 2023 Aug 1]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf
4. Klompas M, Kleinman K, Murphy MV. Descriptive epidemiology and attributable morbidity of ventilator-associated events. Infect Control Hosp Epidemiol 2014;35:502-10.
5. Peña-López Y, Ramírez-Estrada S, Rello J. Ventilator-associated events: definitions and uses. Encyclopedia of Respiratory Medicine 2022;523-9.
6. Garcia R, Jendresky L, Colbert L, Bailey A, Zaman M, Majumder M. Reducing ventilator-associated pneumonia through advanced oral-dental care: a 48-month study. Am J Crit Care 2009;18:523-32.
7. Bergmans DC, Bonten MJ, Gaillard CA, Paling JC, van der Geest S, van Tiel FH, et al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 2001;164:382-8.
8. Boyer AF, Schoenberg N, Babcock H, McMullen KM, Micek ST, Kollef MH. A prospective evaluation of ventilator-associated conditions and infection-related ventilator-associated conditions. Chest 2015;147:68-81.
9. Muscedere J, Sinuff T, Heyland DK, Dodek PM, Keenan SP, Wood G, et al. The clinical impact and preventability of ventilator-associated conditions in critically ill patients who are mechanically ventilated. Chest 2013;144:1453-60.
10. Bo H, He L, Qu J. Influence of the subglottic secretion drainage on the morbidity of ventilator associated pneumonia in mechanically ventilated patients. Zhonghua Jie He He Hu Xi Za Zhi 2000;23:472-4.
11. Paju S, Scannapieco FA. Oral biofilms, periodontitis, and pulmonary infections. Oral Dis 2007;13:508-12.
12. Fields LB. Oral care intervention to reduce incidence of ventilator-associated pneumonia in the neurologic intensive care unit. J Neurosci Nurs 2008;40:291-8.
13. Sole ML, Talbert S, Yan X, Penoyer D, Mehta D, Bennett M, et al. Impact of deep oropharyngeal suctioning on microaspiration, ventilator events, and clinical outcomes: a randomized clinical trial. J Adv Nurs 2019;75:3045-57.
14. Atashi V, Yousefi H, Mahjobipoor H, Bekhradi R, Yazdannik A. Effect of oral care program on prevention of ventilator-associated pneumonia in intensive care unit patients: a randomized controlled trial. Iran J Nurs Midwifery Res 2018;23:486-90.
15. Sutiono AB, Arifin MZ, Adhipratama H, Hermanto Y. The utilization of APACHE II score to predict the incidence of ventilator-associated pneumonia in patients with severe traumatic brain injury: a single-center study. Interdiscip Neurosurg 2022;28:101457.
16. Nakahashi S, Imai H, Imanaka H, Ohshimo S, Satou T, Shima M, et al. Ventilator-associated events: prevalence and mortality in Japan. J Thorac Dis 2018;10:6942-9.
17. Alipour N, Toulabi T, Manouchehrian N, Anbari K, Rahimi Bashar F. A comparison of the effect of open and close endotracheal suctioning on the hemodynamic status of patient with head trauma hospitalized in the intensive care unit. Evid Based Care 2014;3:65-74.
18. Ebrahimi Fakhar HR, Rezaei K, Kohestani HR. Effect of closed endotracheal suction on incidence of ventilator-associated pneumonia. Sci J Kurdistan Univ Med Sci 2010;15:79-87.
19. Hamishekar H, Shadvar K, Taghizadeh M, Golzari SE, Mojtahedzadeh M, Soleimanpour H, et al. Ventilator-associated pneumonia in patients admitted to intensive care units, using open or closed endotracheal suctioning. Anesth Pain Med 2014;4:e21649.

20. Qi L, Guo X, Nie C, Lv X, Zhang M. Research on effects of oropharyngeal aspiration on incidence of ventilator-associated pneumonia in patients with cerebral hemorrhage in ICU. J Healthc Eng 2022;2022:6433666.
21. Klompas M. Potential strategies to prevent ventilator-associated events. Am J Respir Crit Care Med 2015;192:1420-30.
22. Gershonovitch R, Yarom N, Findler M. Preventing ventilator-associated pneumonia in intensive care unit by improved oral care: a review of randomized control trials. SN Compr Clin Med 2020;2:727-33.
23. Klein Klouwenberg PM, van Mourik MS, Ong DS, Horn J, Schultz MJ, Cremer OL, et al. Electronic implementation of a novel surveillance paradigm for ventilator-associated events: feasibility and validation. Am J Respir Crit Care Med 2014;189:947-55.
24. Bouadma L, Sonneville R, Garrouste-Orgeas M, Darmon M, Souweine B, Voiriot G, et al. Ventilator-associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. Crit Care Med 2015;43:1798-806.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):469-478
https://doi.org/10.4266/acc.2023.00430

| pISSN 2586-6052 | eISSN 2586-6060

Palliative care knowledge and attitudes toward end-of-life care among intensive care unit nurses in Jordan

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Background: There is a growing need for palliative care globally due to the rapid aging of the population and improvement in cancer survival rates. Adequate knowledge and a positive attitude are vital for palliative care nurses. The study's purpose was to examine nurses' knowledge and attitudes toward palliative care.

Methods: A cross-sectional design with convenience sampling was used. The study included 182 intensive care unit (ICU) nurses from Jordanian hospitals in all sectors. Self-administered questionnaires were used to assess nurses' knowledge and attitudes toward palliative care. Descriptive statistics, analysis of variance, and the Kruskal-Wallis H test were used to analyze the data.

Results: We measured nurses' knowledge using the Palliative Care Quiz for Nursing, and we measured nurses' attitudes using the Frommelt Attitude Toward Care of the Dying scale. The mean total knowledge and attitude scores were 8.88 (standard deviation [SD], 2.52) and 103.14 (SD, 12.31), respectively. The lowest level of knowledge was in psychosocial and spiritual care (mean±SD, 0.51±0.70). The percentage of nurses with unfavorable attitudes was 53.3%. Significant differences in knowledge and attitude levels were observed according to educational level, experience, and hospital type.

Conclusions: ICU nurses have insufficient knowledge and inappropriate attitudes toward palliative care. Knowledge of psychological and spiritual aspects of palliative care was particularly lacking as were appropriate attitudes towards communication with dying patients. Improving knowledge and attitudes toward palliative care in nursing schools and hospitals would help overcome this problem.

Key Words: attitudes; Jordan; knowledge; nurses; palliative care

Original Article

Received: February 15, 2023
Revised: April 26, 2023
Accepted: August 3, 2023

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INTRODUCTION

Palliative care is an integrated health approach aimed at relieving suffering in those with serious health problems by identifying and treating physical, psychological, social, or spiritual problems [1]. According to the World Health Organization, 40 million people require

palliative care each year, 78% of whom reside in low- and middle-income nations. This need for palliative care is expected to increase due to the increase in the older population and the burden of communicable and non-communicable diseases [2]. Only one in ten of those requiring palliative care services are receiving these services [3]. Previous studies found that early delivery of palliative care reduces hospital admissions and healthcare costs [4,5].

A multidisciplinary team provides palliative care, including nurses, physicians, physiotherapists, pharmacists, and others [6]. Among healthcare professionals, nurses spend the greatest amount of time with patients suffering serious illnesses and their families [7]. Nurses' knowledge and attitudes toward palliative care affect their willingness and competence to provide quality patient care [8-10]. However, many studies have shown that nurses have insufficient knowledge and unfavorable attitudes towards palliative care [11-14].

We used the Palliative Care Quiz for Nursing (PCQN) to assess nurses' knowledge about palliative care. Other researchers have also used the PCQN to quantify nurses' palliative care knowledge. Iranmanesh et al. [11] assessed palliative care knowledge among a sample of oncology and intensive care unit (ICU) nurses in Iran and found the PCQN mean score was 7.59 (standard deviation [SD], 2.28), indicating that nurses had insufficient knowledge. The management of pain and other symptoms dimension (46.07%) had the most accurate responses. The psychological and spiritual care factor had the fewest correct responses (19.3%). Aso, no correlation was found between nurses' knowledge and attitudes toward palliative care [15]. Another study using the PCQN was conducted in Greece. The knowledge level of nurses in a major public hospital was assessed. The mean PCQN score was 8.9 (SD, 2.6), indicating poor knowledge. The same study found that nurses' palliative care knowledge was significantly associated with gender, age, work experience, and level of education [16]. In a study conducted in Ethiopia, most nurses had insufficient palliative care knowledge; the mean PCQN score was 9.34. Nurses' experience was associated with nurses' palliative care knowledge [17]. In China, in a study that included nurses from oncology departments, the PCQN mean was 10.3 (SD, 1.9), which was increased to 11.1 (SD, 2.2) as a result of a palliative care training intervention [12]. Another study that included nurses working in a facility for the elderly in Ireland found that the mean PCQN score was 11.85 (SD, 2.82). The study also examined nurses' attitudes toward palliative care using the thanatophobia scale and found that palliative knowledge significantly correlated with attitudes towards palliative care and years of experience [13]. In a survey that included nurses from Addis Ababa hospitals, only 30.5% had solid palliative care knowledge [18]. Another study conducted in Iran found that 19.3%, 56.1%, and 24.6% of the nurses were reported to have good, moderate, and poor levels of palliative care knowledge, respectively [19]. The PCQN was also used in a study that included 122 nurses in Nepal. There the mean PCQN was 8.82 (SD, 1.95). Only 29.5% had adequate knowledge; the remaining 70.5% had poor knowledge. No significant correlation was found between nurses' knowledge and attitudes toward palliative care [14] in that study. However, Chover-Sierra et al. [20] examined the palliative care knowledge of nurses in Spain and found that nurses had sufficient knowledge. Significant differences in palliative care knowledge were found in relation to nurses' level of education and experience in palliative care. Similarly, another study that included nurses from Ethiopia found that 62.8% had good palliative care knowledge [21]. The results of these studies indicate a wide range of nursing knowledge in different settings, policies, and cultures. Therefore, we believe in the importance of examining the level of knowledge of ICU nurses in Jordanian hospitals.

We used the Frommelt Attitude Toward Care of the Dying (FATCOD) scale to measure nurses' attitudes toward palliative care. This scale has been used in many other studies. Hao et al. [12] found that the FATCOD mean increased from 100.6 (SD, 7.9) to 102.9 (SD, 8.9) after the application of a training intervention. In another study, the mean total FATCOD score was 74.98 (SD, 8.18); 85.3% of the nurses had favorable attitudes toward palliative care, and only 14.7% had unfavorable attitudes toward palliative care. Nursing attitudes toward palliative care were significantly associated with the nurse's level of education [19]. Kassa et al. [18] found that 259 (76%) nurses

KEY MESSAGES

- Intensive care unit (ICU) nurses in this study have insufficient palliative care knowledge, and >50% of the nurses had unfavorable attitudes toward palliative care.
- Attitudes of ICU nurses toward end-of-life care positively and highly correlated with their palliative care knowledge.
- Nurses' palliative care knowledge significantly differed based on their level of education, hospital sector, and ICU years of experience.

had a favorable attitude toward palliative care. Hospital type and nurses' education level were also significantly associated with the nurses' attitudes. However, another study conducted in Ethiopia found that the mean total FATCOD score was 79.58 (SD, 6.33). More than half (51.8%) of the nurses held unfavorable attitudes toward palliative care. Nurses' experience was significantly associated with nurses' attitudes toward palliative care [17]. Also, another study in which nursing attitudes were associated with years of experience, found that 43.7% of the nurses had unfavorable attitudes toward palliative care [21]. In a study conducted in Nepal, most nurses (71.3%) had unfavorable attitudes toward palliative care. The mean FATCOD score was 107.36 (SD, 9.17) [14]. Nurses' attitudes toward palliative care were inconsistent in previous studies, ranging from unfavorable to favorable attitudes. This indicates the need to examine attitudes and factors that may affect these attitudes within a Middle Eastern cultural context.

In Jordan, the introduction of palliative care was started along with the launching of the Jordan Palliative Care Initiative in 2001. As a result of this initiative, nurses were recognized as part of the multidisciplinary palliative care team and received training and educational activities related to palliative care. Despite that initiative, no national palliative care policy is currently in place in Jordan. This leaves many cancer patients in Jordan without access to necessary palliative care services [22]. In Jordan, only a few studies have examined knowledge and attitudes toward palliative care; and those studies were among nursing students. Al Qadire [23] used the PCQN to examine nursing students' palliative care knowledge. The mean PCQN was low (mean, 8.0; SD, 3.1). Another study by Zahran et al. [24] assessed nursing students' attitudes toward death and caring for dying patients. Nursing students held positive attitudes toward studied concepts. Examining nurses' knowledge and attitudes toward palliative care is essential to inform policymakers and nurse managers on areas that need improvement. Thus, this study aimed to examine ICU nurses' palliative care knowledge and their attitudes toward end-of-life (EOL) care and to determine if the two are correlated. Moreover, this study assessed the differences in ICU nurses' palliative care knowledge and their attitudes toward EOL care based on selected characteristics of the nurses.

MATERIALS AND METHODS

Design and Setting

A correlational cross-sectional design was used in this study. The study was conducted in Jordanian hospitals. Jordanian hospitals are classified based on the healthcare sector: private hospitals (57%), governmental hospitals (30%), military hospitals (11%), and university hospitals (2%.) All Jordanian hospitals that contain ICUs were targeted in this study.

Sample and Sampling

A convenience sampling technique was used to include 182 ICU nurses from Jordanian hospitals. The inclusion criteria for nurses were being a full-time registered nurse and having at least 1 year of ICU experience. The G-power program 3.0.10. was used to calculate the required sample size. The F test was utilized using an alpha level of 0.05, a medium effect size of 0.25, and a power of 0.8. The estimated required sample size was at least 180 ICU nurses.

Ethical Considerations

The Scientific and Research Committee at the affiliated institution approved the study. Since the data collection took place through an electronic self-administered questionnaire using networking and snowballing, institutional approval for this study was not required. The survey included a description that provides the participant information about the study purpose, data collection procedure, and rights of the participants, followed by a consent statement that required participant completion before answering the instrument questions. Participation was entirely voluntary, and participants were assured that their responses would be confidential. Confidentiality was ensured throughout the study. Data were secured in a password-protected computer. The front page of the questionnaire contains the study objectives, confidentiality issues, and anonymity and privacy statements for the respondents. The authors granted permission for the use of the questionnaires.

Data Collection

Data collection began after obtaining ethical approval. A computerized self-administered questionnaire was used to collect the data. Networking and snowballing techniques were used to reach the target population. Also, nurses' social media groups were used to distribute the questionnaire. Google Forms was used for data collection, and all submitted questionnaires were automatically saved in the researcher's private Google Drive. Data collection took place between March 2021 and October 2021.

Measures

Demographic information

This information was acquired through questions on participants' age, years of experience in the ICU, total years of experience, gender, level of education, and hospital sector.

Palliative care knowledge

This was measured using the PCQN developed by Ross et al. [25]. The PCQN comprises 20 questions with three possible responses: true, false, or do not know. Scores were obtained by summing the correct answers. The range of total possible scores was from 0 to 20. Higher scores corresponded to higher levels of palliative care knowledge. The PCQN is subdivided into three theoretical dimensions: pain and symptoms management (items 2–4, 6–8, 10, 13–16, 18, and 20), philosophy and principles of palliative care (items 1, 9, 12, and 17), and psychosocial and spiritual care (items 5, 11, and 19) [25,26]. The tool's validity and reliability were previously ensured; a 0.78 internal consistency was demonstrated [25]. In this study, Cronbach's alpha coefficient was 0.72.

Attitudes toward EOL care

This was measured using the Frommelt Attitude Toward Care of the Dying (FATCOD) scale developed by Frommelt [27]. The tool is composed of 30 items using a five-point Likert scale to indicate respondents' attitudes toward caring for dying patients. The scale consists of an equal number of positively and negatively worded statements. The response options were strongly disagree, disagree, uncertain, agree, and strongly agree (1, 2, 3, 4, and 5, respectively) for positive items. Negative items were reverse coded and appear in Table 1. The total possible score ranges from 30 to 150. A higher score indicated a more positive attitude toward caring for dying patients. The scale showed a satisfactory Cronbach's alpha coefficient of 0.75 [28]. In this study, Cronbach's alpha coefficient was 0.82.

Data Analysis

Data were analyzed using the IBM SPSS ver. 24 (IBM Corp.). Preliminary data analysis was conducted to describe the demographic data of the study sample via the mean and SD. The t-test, analysis of variance, and Kruskal-Wallis H test were used to examine and compare participants' knowledge of palliative care, attitudes toward EOL care, and demographic factors.

RESULTS

The sample comprised 182 ICU nurses. The individuals' average age was 30.3 years (SD, 6.2 years), and their average experience in the ICU was 4.9 years (SD, 4.4 years). The majority were females (51.1%), had a bachelor's degree (75.8%), and worked in a private hospital (54.9%). Table 2 shows more details about participants' demographics and other relevant characteristics.

Table 3 shows the responses of ICU nurses toward palliative care knowledge. The mean total PCQN score was 8.88 (SD, 2.52). The majority of the nurses correctly answered that adjuvant therapies are important in managing pain (80%), individuals who are taking opioids should also follow a bowel regime (79.1%), and morphine is the standard used to compare the analgesic effect of other opioids (77.5%). This shows that the three highest reported correct responses were related to the pain and symptoms management domain. Most nurses incorrectly answered questions about caregiver "burnout" (12.6%); family presence during death (14.3%); and the relationship between the degree of loss feelings and type of bond, distant or close, to the deceased (14.3%).

Table 1 demonstrates the attitudes of ICU nurses toward EOL care. The mean total FATCOD score was 103.14 (SD, 12.31). The most positive (favorable) attitudes among the ICU nurses included talking about permitting dying patients more resilient schedule of visits (77.5%), family involvement in providing care to the patient (76.9%), the importance for the dying person to verbalize his/her feelings (76.9%), and the importance of the learning experience gained from giving nursing care to the dying person (76.4%). However, the most negative (unfavorable) attitudes appeared when nurses agreed with not feeling comfortable seeing the terminally ill patient when entering his/her room (64.8%). Also, the nurses did not feel comfortable talking with dying patients about death (55.5%), nurses felt upset if their dying patients lose hope (57.1%), and the nurses believed that someone else should talk with the dying patients about death (54.4%). The percentage of disagreement with a positive attitude was 53.3%.

ICU nurses' knowledge of palliative care and their attitudes toward EOL care were significantly and positively correlated ($r=0.215$, $P<0.01$). In addition, Table 4 demonstrates the differences in palliative care knowledge and attitudes toward EOL care according to ICU nurses' demographics. Palliative care knowledge significantly differed based on the level of education, hospital sector, and ICU years of experience, while

Table 1. Attitudes of ICU nurses toward end-of-life care (FATCOD scale) (n=182)

Item	Disagreement (strongly disagree & disagree)	Neutral	Agreement (agree & strongly agree)
1. Giving nursing care to the dying person is a worthwhile learning experience.	25 (13.7)	18 (9.9)	139 (76.4)
2. Death is not the worst thing that can happen to a person.	41 (22.5)	54 (29.7)	87 (47.8)
3. I would be uncomfortable talking about impending death with the dying person.[a]	28 (15.4)	53 (29.1)	101 (55.5)
4. Nursing care for the patient's family should continue throughout the period of grief and bereavement.	24 (13.2)	29 (15.9)	129 (70.9)
5. I would not want to be assigned to care for a dying person.[a]	69 (37.9)	58 (31.9)	55 (30.2)
6. The nurse should not be the one to talk about death with the dying person.[a]	36 (19.8)	47 (25.8)	99 (54.4)
7. The length of time required to give nursing care to a dying person would frustrate me.[a]	60 (33.0)	52 (28.6)	70 (38.5)
8. I would be upset when the dying person I was caring for gave up hope of getting better.[a]	21 (11.5)	57 (31.3)	104 (57.1)
9. It is difficult to form a close relationship with the family of a dying person.[a]	59 (32.4)	36 (19.8)	87 (47.8)
10. There are times when death is welcomed by the dying person.	50 (27.5)	45 (24.7)	87 (47.8)
11. When a patient asks, "Nurse am I dying?", I think it is best to change the subject to something cheerful.[a]	58 (31.9)	32 (17.6)	92 (50.5)
12. The family should be involved in the physical care of the dying person.	25 (13.7)	17 (9.3)	140 (76.9)
13. I would hope the person I'm caring for dies when I am not present.[a]	45 (24.7)	58 (31.9)	79 (43.4)
14. I am afraid to become friends with a dying person.[a]	47 (25.8)	43 (23.6)	92 (50.5)
15. I would feel like running away when the person actually died.[a]	69 (37.9)	41 (22.5)	72 (39.6)
16. Families need emotional support to accept the behavior changes of the dying person.	19 (10.4)	25 (13.7)	99 (54.4)
17. As a patient nears death, the nurse should withdraw from his/her involvement with the patient.[a]	87 (47.8)	34 (18.7)	61 (33.5)
18. Families should be concerned about helping their dying member make the best of his/her remaining life.	18 (9.9)	28 (15.4)	8136 (74.7)
19. The dying person should not be allowed to make decisions about his/her physical care.[a]	92 (50.5)	41 (22.5)	49 (26.9)
20. Families should maintain as normal an environment as possible for their dying member.	18 (9.9)	29 (15.9)	135 (74.2)
21. It is beneficial for the dying person to verbalize his/her feelings.	14 (7.7)	28 (15.4)	140 (76.9)
22. Nursing care should extend to the family of the dying person.	23 (12.6)	35 (19.2)	124 (68.1)
23. Nurses should permit dying persons to have flexible visiting schedules.	15 (8.2)	26 (14.3)	141 (77.5)
24. The dying person and his/her family should be the in-charge decision-makers.	28 (15.4)	47 (25.8)	107 (58.8)
25. Addiction to pain relieving medication should not be a nursing concern when dealing with a dying person.	41 (22.5)	51 (28.0)	90 (49.5)
26. I would be uncomfortable if I entered the room of a terminally ill person and found him/her crying.[a]	32 (17.6)	32 (17.6)	117 (64.8)
27. Dying persons should be given honest answers about their condition.	20 (11.0)	62 (34.1)	100 (54.9)
28. Educating families about death and dying is not a nursing responsibility.[a]	57 (31.3)	58 (31.9)	67 (36.8)
29. Family members who stay close to a dying person often interfere with the professionals' job with the patient.[a]	38 (20.9)	56 (30.8)	88 (48.4)
30. It is possible for nurses to help patients prepare for death.	28 (15.4)	58 (31.9)	96 (52.7)
Scale		Mean±SD	Median (IQR)
FATCOD total score		103.14±12.31	103.00 (97.00–109.25)

Values are presented as number (%) unless otherwise indicated.
ICU: intensive care unit; FATCOD: Frommelt Attitude Toward Care of the Dying; SD: standard deviation; IQR: interquartile range.
a) Negative items were reverse coded.

attitudes toward EOL care significantly differed based on the level of education and hospital sector. Finally, palliative care knowledge and attitudes toward EOL did not significantly differ based on the nurses' gender.

DISCUSSION

This study examined palliative care knowledge and attitudes of ICU nurses in Jordanian hospitals. The results showed that

Table 2. Participants characteristics (n=182)

Characteristics	Value (n=182)
Age (yr)	30.3±6.2
<30	97 (53.3)
30–39	66 (36.3)
≥40	19 (10.4)
Total years of nursing experience	7.8±6.0
ICU years of experience	4.9±4.4
1	51 (28.0)
2–5	73 (40.1)
6–9	28 (15.4)
≥10	30 (16.5)
Sex	
Male	89 (48.9)
Female	93 (51.1)
Level of education	
Diploma	5 (2.7)
Bachelor	139 (75.8)
Master	34 (18.7)
PhD	5 (2.7)
Hospital sector	
Governmental	51 (28.0)
Private	100 (54.9)
Military	11 (6.0)
Educational	20 (11.0)

Values are presented as mean±standard deviation or number (%).
ICU: intensive care unit; PhD: doctor of philosophy.

these nurses have insufficient levels of knowledge. However, the levels of pain and symptom management knowledge were the highest across the three dimensions. The majority of the nurses had unfavorable attitudes about palliative care, including communication with a dying patient and the nursing role in talking about death. Palliative care knowledge differed significantly according to the level of education, hospital type, and years of experience. Attitudes toward palliative care differed significantly based on the level of education and hospital type.

ICU nurses' knowledge of palliative care in this study was consistent with the findings of Iranmanesh et al. [11], Razban et al. [15], Maria et al. [16], and Etafa et al. [17] on samples of nurses in Iran, Greece, and Ethiopia. All results of these studies agreed with the current study by reporting insufficient palliative care knowledge. In Jordan, the undergraduate nursing curriculum does not address palliative care subjects and topics. These topics are sometimes integrated into other undergraduate nursing subjects. This might explain the nurses' insufficient knowledge of palliative care. In addition, palliative care services are provided by only two institutions in the capital, Amman, which indicates the scarcity of these services and the lack of knowledge about these services [29].

The current results revealed that the highest levels of palliative care knowledge concerned pain and symptom management, which was consistent with a previous study on palliative care knowledge among nurses in Jordan [30]. In addition, Iranian nurses also showed the highest levels of knowledge in pain and symptom management [15]. This finding could be attributed to the country's emphasis in nursing education on the physical examination that includes managing pain and other symptoms. The poorest knowledge level was in the psychosocial and spiritual care dimension. This indicates the lack of addressing these issues in the nursing schools and hospitals in the country.

The majority of the nurses had unfavorable attitudes toward palliative care. This finding was consistent with the attitudes among nurses in Ethiopia [17]. However, while nurses in the current study showed the most favorable attitudes in some areas of palliative care, such as family involvement in the physical care and the benefits of verbalizing the feelings of a dying person, Etafa et al. [17] indicated better attitudes than ours in the same areas. These favorable attitudes can be attributed to nurses' understanding of the importance of family members' presence and the significance of the dying person's expression of their feelings. Arab culture supports the involvement of family members in caring for a dying person in the family, which indicates the nurses' high level of acceptance of this attitude. The percentage of nurses who felt uncomfortable discussing imminent death with a dying individual in the current study was smaller than the proportion of these poor attitudes observed by Etafa et al. [17]. This outcome can be explained by the evidence that healthcare providers are generally not encouraged to talk about death as these providers feel that dealing with death is a negative side of their profession. Talking about death is perceived as destroying the patient's hope and bringing guilt to the providers. In addition, healthcare providers are hesitant to give bad news to their patients because of the inability to predict the patients' reactions [31].

Nurses with a PhD level of education, nurses with 2–5 years of ICU experience, and nurses who work in educational hospitals showed the significantly highest levels of EOL palliative care knowledge. A previous study [16] indicated that nurses with Master's degrees and nurses with an experience of more than 10 years showed the significantly highest levels of knowledge. In our study, we expected that a higher level

Table 3. Palliative care knowledge of ICU nurses (PCQN scale) (n=182)

Item	Correct answer	Wrong answer
1. Palliative care is appropriate only in situations where there is evidence of a downhill trajectory or deterioration. (F)	56 (30.8)	126 (69.2)
2. Morphine is the standard used to compare the analgesic effect of other opioids. (T)	141 (77.5)	41 (22.5)
3. The extent of the disease determines the method of pain treatment. (F)	31 (17.0)	151 (83.0)
4. Adjuvant therapies are important in managing pain. (T)	147 (80.8)	35 (19.2)
5. It is crucial for family members to remain at the bedside until death occurs. (F)	26 (14.3)	156 (85.7)
6. During the last days of life, the drowsiness associated with electrolyte imbalance may decrease the need for sedation. (T)	101 (55.5)	81 (44.5)
7. Drug addiction is a major problem when morphine is used on a long-term basis for the management of pain. (F)	75 (41.2)	107 (58.8)
8. Individuals who are taking opioids should also follow a bowel regime. (T)	144 (79.1)	38 (20.9)
9. The provision of palliative care requires emotional detachment. (F)	83 (45.6)	99 (54.4)
10. During the terminal stages of an illness, drugs that can cause respiratory depression are appropriate for the treatment for severe dyspnea. (T)	69 (37.9)	113 (62.1)
11. Men generally reconcile their grief more quickly than women. (F)	40 (22.0)	142 (78.0)
12. The philosophy of palliative care is compatible with that of aggressive treatment. (T)	99 (54.4)	83 (45.6)
13. The use of placebos is appropriate in the treatment of some types of pain. (F)	79 (43.4)	103 (56.6)
14. In high doses, codeine causes more nausea and vomiting than morphine. (T)	113 (62.1)	69 (37.9)
15. Suffering and physical pain are synonymous. (F)	42 (23.1)	140 (76.9)
16. Demerol is not an effective analgesic in the control of chronic pain. (T)	90 (49.5)	92 (50.5)
17. The accumulation of losses renders burnout inevitable for those who seek work in palliative care. (F)	23 (12.6)	159 (87.4)
18. Manifestations of chronic pain are different from those of acute pain. (T)	125 (68.7)	57 (31.3)
19. The loss of a distant or contentious relationship is easier to resolve than the loss of one that is close or intimate. (F)	26 (14.3)	156 (85.7)
20. The pain threshold is lowered by anxiety or fatigue. (T)	107 (58.8)	75 (41.2)
Scales/subscales	Mean±SD	Median (IQR)
PCQN total score	8.88±2.52	9.00 (7.75–11.00)
Philosophy and principles of palliative care	1.43±0.84	1.00 (1.00–2.00)
Pain and symptoms management	6.95±2.19	7.00 (6.00–9.00)
Psychosocial and spiritual care	0.51±0.70	0.00 (0.00–1.00)

Values are presented as number (%) unless otherwise indicated.
ICU: intensive care unit; PCQN: Palliative Care Quiz for Nursing; F: false; T: true; SD: standard deviation; IQR: interquartile range.

of education would bring more knowledge. However, the knowledge differences based on experience were inconsistent with previous research. This study also indicated that nurses with PhD degrees and who work in private hospitals showed significantly better attitudes toward EOL care. The significant association between knowledge and attitudes helps explain the better attitude among nurses with PhD degrees. Last, the single private hospital in Jordan that provides specialized palliative care is included in the study. This could contribute to the finding that nurses in private hospitals showed better attitudes [29].

One of the study's drawbacks was utilizing self-administered questionnaires through an online survey. The study employed a cross-sectional design, which prevented identification of causal relationships. Future qualitative research might help understand this phenomenon. The knowledge and attitudes of nurses with a doctoral degree were higher than nurses with lower educational levels. However, this result should be carefully interpreted as the number of nurses with a doctoral degree in this study was small.

This study showed that ICU nurses have insufficient palliative care knowledge and inappropriate attitudes. The lowest levels of knowledge were in psychological and spiritual care, while the poor attitudes were found in communication with a dying patient, particularly in talking about death. Improving palliative care knowledge would help enhance appropriate attitudes toward palliative care. Nursing educational institutions should focus on palliative care within the nursing

Table 4. Comparison of PCQN and FATCOD scores across participants' characteristics (n=182)

Characteristics	n	Mean±SD	Rank mean	Kruskal-Wallis H	df	P-value
PCQN score						
Age (yr)				0.05	2	0.977
<30	97	8.9±2.5	92.2			
30–39	66	8.8±2.6	90.9			
≥40	19	9.0±2.6	89.9			
Level of education				7.80	3	0.050
Diploma	5	10.2±2.1	120.6			
Bachelor	138	8.7±2.6	88.4			
Master	34	9.0±2.0	91.4			
PhD	5	11.6±2.2	147.6			
ICU's years of experience				12.33	3	0.006
1	51	8.1±2.2	71.7			
2–5	73	9.3±2.9	103.5			
6–9	28	9.5±1.6	101.0			
≥10	30	8.7±2.4	87.1			
Type of hospital				9.44	3	0.024
Governmental	51	8.1±2.7	75.5			
Private	100	9.3±2.4	99.8			
Military	11	8.2±2.2	72.8			
Educational	20	9.4±2.2	101.4			
FATCOD score						
Age (yr)				2.86	2	0.239
< 30	97	103.7±9.8	94.3			
30–39	66	101.1±15.0	83.7			
≥40	19	107.4±12.7	104.5			
Level of education				12.98	3	0.005
Diploma	5	102.4±5.2	85.3			
Bachelor	138	102.6±12.8	89.7			
Master	34	102.8±9.7	87.4			
PhD	5	122.2±3.2	174.9			
ICU's years of experience				1.54	3	0.673
1	51	102.0±9.1	86.2			
2–5	73	103.5±14.7	94.1			
6–9	28	103.9±9.2	99.3			
≥10	30	103.6±13.5	86.9			
Type of hospital				7.86	3	0.049
Governmental	51	101.6±12.0	84.5			
Private	100	105.0±13.4	100.8			
Military	11	100.0±10.2	75.5			
Educational	20	100.2±6.9	71.7			

PCQN: Palliative Care Quiz for Nursing; PhD: doctor of philosophy; FATCOD: Frommelt Attitude Toward Care of the Dying; SD: standard deviation; ICU: intensive care unit.

curricula. In addition, hospitals are required to add palliative care topics to their continuous education strategies to ensure that nurses have adequate competency to provide this type of nursing care. Future studies that compare nurses who work in hospitals offering palliative care services to nurses from hospitals that do not provide these services are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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REFERENCES

1. World Health Organization. Health topics: palliative care [Internet]. World Health Organization; 2023 [cited 2023 Aug 1]. Available from: https://www.who.int/health-topics/palliative-care
2. World Health Organization. Palliative care [Internet]. World Health Organization; 2020 [cited 2023 Aug 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/palliative-care
3. Canadian Hospice Palliative Care Association. Global atlas highlights unmet need for palliative care [Internet]. Canadian Hospice Palliative Care Association; 2014 [cited 2023 Aug 1]. Available from: https://www.chpca.ca/news/global-atlas-highlights-unmet-need-for-palliative-care/
4. Seow H, Sutradhar R, Burge F, McGrail K, Guthrie DM, Lawson B, et al. End-of-life outcomes with or without early palliative care: a propensity score matched, population-based cancer cohort study. BMJ Open 2021;11:e041432.
5. Zemplényi AT, Csikós Á, Fadgyas-Freyler P, Csanádi M, Kaló Z, Pozsgai É, et al. Early palliative care associated with lower costs for adults with advanced cancer: evidence from Hungary. Eur J Cancer Care (Engl) 2021;30:e13473.
6. Bowen L. The multidisciplinary team in palliative care: a case reflection. Indian J Palliat Care 2014;20:142-5.
7. Schroeder K, Lorenz K. Nursing and the future of palliative care. Asia Pac J Oncol Nurs 2018;5:4-8.
8. Chen L, Li XH, Pan X, Pan QN, Huang HQ, Tao PY, et al. Nurses' knowledge, attitudes, and willingness to practice hospice care: an analysis of influencing factors. PLoS One 2022;17:e0259647.
9. Lin HY, Chen CI, Lu CY, Lin SC, Huang CY. Nurses' knowledge, attitude, and competence regarding palliative and end-of-life care: a path analysis. PeerJ 2021;9:e11864.
10. Shen Y, Nilmanat K, Promnoi C. Palliative care nursing competence of Chinese oncology nurses and its related factors. J Hosp Palliat Nurs 2019;21:404-11.
11. Iranmanesh S, Razban F, Tirgari B, Zahra G. Nurses' knowledge about palliative care in Southeast Iran. Palliat Support Care 2014;12:203-10.
12. Hao Y, Zhan L, Huang M, Cui X, Zhou Y, Xu E. Nurses' knowledge and attitudes towards palliative care and death: a learning intervention. BMC Palliat Care 2021;20:50.
13. Wilson O, Avalos G, Dowling M. Knowledge of palliative care and attitudes towards nursing the dying patient. Br J Nurs 2016;25:600-5.
14. Nepal P, Garbuja CK, Nepal M. Clinical nurses' knowledge and attitude on palliative care: a cross-sectional study. J Lumbini Med Coll 2021;9:7.
15. Nepal P, Garbuja C, Nepal M. Clinical nurses' knowledge and attitude on palliative care: a cross-sectional study. J Lumbini Med Coll 2021;9:7.
16. Razban F, Tirgari B, Iranmanesh S. Nurses' knowledge about and attitude towards palliative care in Southeast Iran. Asian J Nurs Educ Res 5(3): 2015;5:399-404.
17. Etafa W, Wakuma B, Fetensa G, Tsegaye R, Abdisa E, Oluma A, et al. Nurses' knowledge about palliative care and attitude towards end-of-life care in public hospitals in Wollega zones: multicenter cross-sectional study. PLoS One 2020;15:e0238357.
18. Kassa H, Murugan R, Zewdu F, Hailu M, Woldeyohannes D. Assessment of knowledge, attitude and practice and associated factors towards palliative care among nurses working in selected hospitals, Addis Ababa, Ethiopia. BMC Palliat Care 2014;13:6.

19. Farmani AH, Mirhafez SR, Kavosi A, Moghadam Pasha A, Jamali Nasab A, Mohammadi G, et al. Dataset on the nurses' knowledge, attitude and practice towards palliative care. Data Brief 2018;22:319-25.
20. Chover-Sierra E, Martínez-Sabater A, Lapeña-Moñux Y. Knowledge in palliative care of nursing professionals at a Spanish hospital. Rev Lat Am Enfermagem 2017;25:e2847.
21. Zeru T, Berihu H, Gerensea H, Teklay G, Teklu T, Gebrehiwot H, et al. Assessment of knowledge and attitude towards palliative care and associated factors among nurses working in selected Tigray hospitals, northern Ethiopia: a cross-sectional study. Pan Afr Med J 2020;35:121.
22. Omran S, Obeidat R. Palliative care nursing in Jordan. J Palliat Care Med 2015;S4:005.
23. Al Qadire M. Knowledge of palliative care: an online survey. Nurse Educ Today 2014;34:714-8.
24. Zahran Z, Hamdan KM, Hamdan-Mansour AM, Allari RS, Alzayyat AA, Shaheen AM. Nursing students' attitudes towards death and caring for dying patients. Nurs Open 2022;9:614-23.
25. Ross MM, McDonald B, McGuinness J. The palliative care quiz for nursing (PCQN): the development of an instrument to measure nurses' knowledge of palliative care. J Adv Nurs 1996;23:126-37.
26. Kim JS, Kim J, Gelegjamts D. Knowledge, attitude and self-efficacy towards palliative care among nurses in Mongolia: a cross-sectional descriptive study. PLoS One 2020;15:e0236390.
27. Frommelt KH. The effects of death education on nurses' attitudes toward caring for terminally ill persons and their families. Am J Hosp Palliat Care 1991;8:37-43.
28. Mastroianni C, Piredda M, Taboga C, Mirabella F, Marfoli E, Casale G, et al. Frommelt attitudes toward care of the dying scale form B: psychometric testing of the Italian version for students. Omega (Westport) 2015;70:227-50.
29. Stjernswärd J, Ferris FD, Khleif SN, Jamous W, Treish IM, Milhem M, et al. Jordan palliative care initiative: a WHO Demonstration Project. J Pain Symptom Manage 2007;33:628-33.
30. Al Qadire M. Nurses' knowledge about palliative care: a cross-sectional survey. J Hosp Palliat Nurs 2014;16:23-30.
31. Warnock C. Breaking bad news: issues relating to nursing practice. Nurs Stand 2014;28:51-8.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):479-487
https://doi.org/10.4266/acc.2023.00990

| pISSN 2586-6052 | eISSN 2586-6060

The effects of environmental interventions for delirium in critically ill surgical patients

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Background: Delirium occurs at high rates among patients in intensive care units and increases the risk of morbidity and mortality. The purpose of this study was to investigate the effects of environmental interventions on delirium.

Methods: This prospective cohort study enrolled 192 patients admitted to the surgical intensive care unit (SICU) during the pre-intervention (June 2013 to October 2013) and post-intervention (June 2014 to October 2014) periods. Environmental interventions involved a cognitive assessment, an orientation, and a comfortable environment including proper sleep conditions. The primary outcomes were the prevalence, duration, and onset of delirium.

Results: There were no statistically significant differences in incidence rate, time of delirium onset, general characteristics, and mortality between the pre-intervention and post-intervention groups. The durations of delirium were 14.4±19.1 and 7.7±7.3 days in the pre-intervention and post-intervention groups, respectively, a significant reduction (P=0.027). The lengths of SICU stay were 20.0±22.9 and 12.6±8.7 days for the pre-intervention and post-intervention groups, respectively, also a significant reduction (P=0.030).

Conclusions: The implementation of an environmental intervention program reduced the duration of delirium and length of stay in the SICU for critically ill surgical patients.

Key Words: critical care; delirium; intensive care unit; length of stay

Original Article

Received: July 28, 2023
Revised: November 4, 2023
Accepted: November 10, 2023

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INTRODUCTION

Delirium is a neuropsychiatric syndrome characterized by cognitive dysfunction, a decreased ability to maintain attention, and unorganized thinking owing to several factors [1]. The incidence rate of delirium is 20%–30% among patients hospitalized in the general ward and 36%–44% among older post-surgery patients [2,3]. However, the incidence rate among patients in intensive care units (ICUs) can approach 70%–90% [4-6]. Delirium has been associated with a prolonged hospital stay, more frequent complications, increased cost of care and duration of mechanical ventilator use, chronic impairment of cognitive function, and mortality [6-8].

Several studies reported that an estimated 30%–40% of delirium cases are preventable [2,9]. However, preventive measures are often not implemented because of advanced patient age,

poor baseline cognition, and patient fragility. Inouye [1] identified four predisposing factors (cognitive impairment, severe illness, visual impairment, and dehydration) and five precipitating factors (polypharmacy, catheterization, use of restraints, malnutrition, and any iatrogenic event) associated with the development of delirium [6,10]. Their results suggest that patients with high baseline vulnerability can develop delirium in response to weak precipitants.

The most frequently debated factor that influences delirium onset is the ICU environment [2]. Crucial factors relevant to the development of delirium include (1) separation from family and acquaintances, (2) a mechanized environment for treatment, (3) noise, (4) bright lights, (5) insufficient sleep, (6) no guaranteed privacy, (7) an environment without windows, where the day is indistinguishable from the night, and (8) movement limitations owing to the numerous catheters required for monitoring and treatment [11].

In the ICU, the main treatment of delirium involves pharmacological intervention [12,13]. Non-pharmacological intervention requires a multi-disciplinary approach; therefore, implementing non-pharmacological interventions in ICU settings can be challenging. However, several studies have reported that non-pharmacological interventions can prevent delirium in ICU patients more effectively than pharmacological interventions [6,13-15]. Delirium frequently occurs in the surgical intensive care unit (SICU) and has been reported to have a negative effect on prognosis in several studies [16]. However, there are not many studies demonstrating the effectiveness of environmental interventions specifically in critically ill surgical patients, a group that experiences a high incidence of delirium. In the present study, we describe results of non- pharmacological environmental interventions targeting critically ill patients admitted to the SICU and investigated whether these interventions improved outcomes associated with delirium.

KEY MESSAGES

- Environmental interventions can help reduce the duration of delirium.
- Environmental interventions in the intensive care unit are safe and effective.

MATERIALS AND METHODS

Study Design

This prospective, pre-post intervention cohort study was performed to assess the impact of an environmental intervention program on critically ill surgical patients (such as those with postoperative trauma and sepsis) who were admitted to the SICU of Asan Medical Center, a tertiary academic teaching hospital with over 2,000 beds. The SICU has 14 beds and is attended by physicians (1 attending, 3 fellows) and registered nurses (staff to patient ratio, 1:2).

This study was approved by the Institutional Review Board of Asan Medical Center (No. 2014-0344). In the intervention group, we obtained written informed consent from the patients and/or the closest family member if a patient could not provide consent. In the control group, we collected data retrospectively and proceeded with a waiver of informed consent. This trial is registered at ClinicalTrials.gov (NCT04042649).

Study Population

The present study enrolled patients admitted to the SICU during the pre-intervention period (June 2013 to October 2013) and post-intervention period (June 2014 to October 2014). Environmental interventions had been applied in the SICU since March 2014, and a 3-month window was decided to consider trial and error in the early stages of the intervention protocol. Inclusion criteria were patients (1) 18 years or older, (2) who understood the purpose of this study and agreed to participate, and (3) who stayed in the SICU for at least 48 hours. Exclusion criteria were patients who (1) remained unresponsive (defined as a Richmond Agitation-Sedation Scale [RASS] score less than –4), (2) could not be assessed by the Confusion Assessment Method for the ICU (CAM-ICU) owing to severe visual or hearing disturbance, (3) had a history of severe psychiatric or neurologic deficits (including delirium before ICU admission), (4) required isolation due to transplantation or immunological compromise, (5) were discharged from the ICU within 48 hours, (6) were re-admitted to the ICU, (7) were younger than 18 years, and (8) were admitted to the SICU through another ICU, because patient transfer also affects delirium.

Delirium Diagnosis

The Society of Critical Care Medicine recommends using the CAM-ICU, developed for critically ill patients, to diagnose delirium [17]. The CAM-ICU has high reliability (93%–100%) and validity (98%–100%), as well as high internal validity [18,19]. The CAM-ICU can be easily administered to critically ill patients on mechanical ventilation [20]. The nurse in charge of each patient applied the CAM-ICU tool using the same meth-

od during the pre- and post-intervention periods and confirmed the development of delirium on each shift (three times per day). To increase accuracy, the presence of delirium was also confirmed by the head nurse. In addition, medical staff training was reinforced via quality improvement (QI) activities.

Delirium Prevention QI Program

The interdisciplinary QI team comprised SICU attending staff, a clinical nurse practitioner, an SICU nurse unit manager, and bedside registered nurses. First, environmental factors that could be improved were identified. During the post-intervention period, we conducted team education on the environmental intervention protocol, analyzed risk factors, and provided feedback on the subsequent outcomes (Figure 1). The environmental interventions were not conducted during the pre-intervention period. However, during the post-intervention period, they were implemented for all patients admitted to the SICU, regardless of delirium diagnosis, and intervention activities were reinforced based on a checklist for task performance. Environmental interventions were performed from the day after SICU admission to discharge from the SICU. The environmental intervention protocol was carried out as described in Figure 2. On the day after SICU admission, a calendar was placed at a site with easy visibility, while an accurate and clear-cut orientation was provided from time, place, and person on every shift. In addition, pictures of the family or close friends were posted, and patients listened to music or watched portable television. A call bell was installed within hands-reach for patients for whom oral communication was difficult owing to tracheal intubation or tracheostomy. Communication was improved by providing glasses and hearing aids to patients with visual and hearing impairments, respectively. A proper sleep environment to improve and promote sleep during the night was created by minimizing nonessential medical activities and providing earplugs and eye masks to be worn as desired [17].

Outcomes and Data Collection

The primary outcomes were prevalence, time to onset, and duration of delirium. Secondary outcomes were number of days of ventilator use, length of SICU stay, length of stay (LOS) at the hospital, rate of SICU readmission, and ICU and in-hospital mortality rates. The relevant data were collected through the electronic medical record system. Average sleep time was

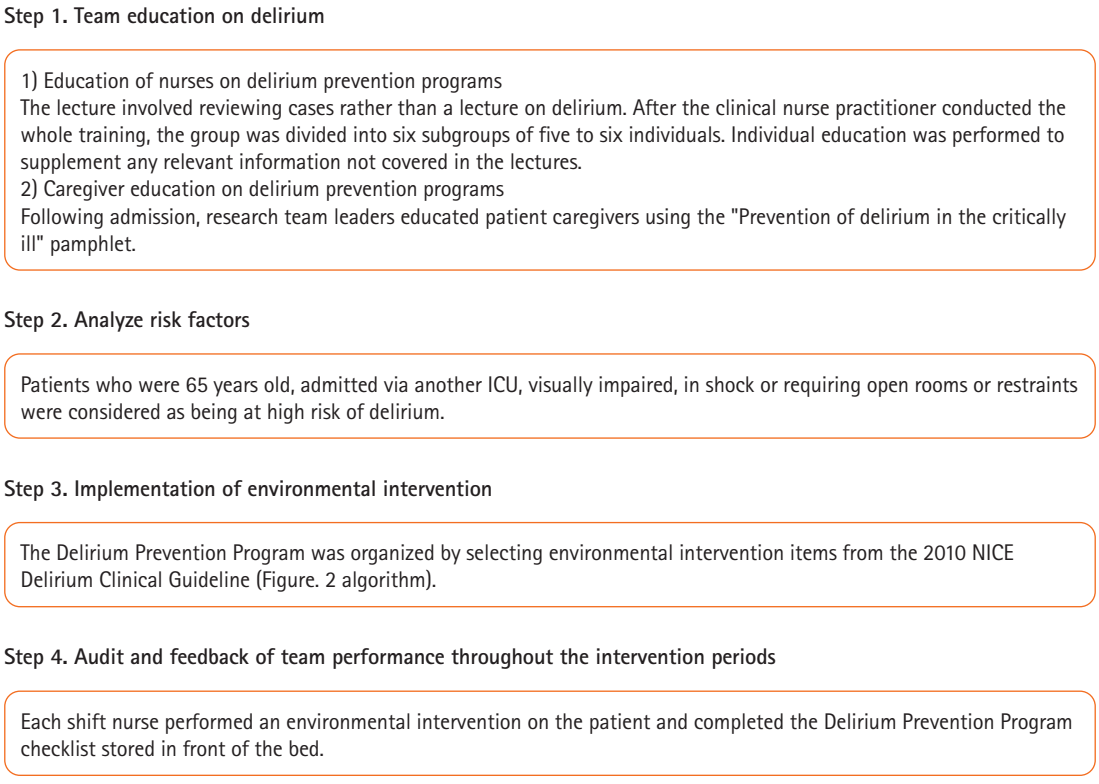

Figure 1. Delirium prevention quality improvement program. ICU: intensive care unit; NICE: National Institute for Health and Care Excellence.

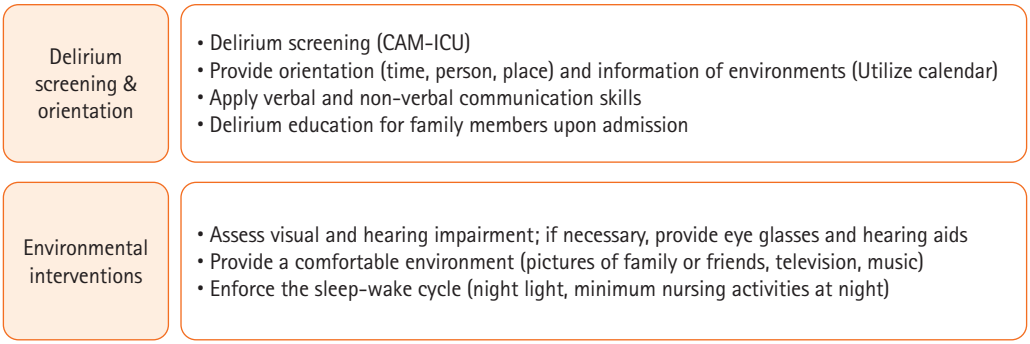

Figure 2. Environmental intervention protocol. CAM-ICU: Confusion Assessment Method for the intensive care unit.

Table 1. General characteristics of included patients (n=184)

Characteristics	Pre-intervention (n=96)	Post-intervention (n=88)	P-value
Male	77 (80.2)	61 (69.3)	0.125
Age (yr)	62±14	64±16	0.334
>65 yr	61 (63.5)	54 (61.4)	0.879
Average sleep time (hr)	6.5±1.6	6.5±1.7	0.154
Sleep disorder	7 (7.3)	6 (6.8)	1.000
Use of sleeping pills	3 (3.1)	6 (6.8)	0.413
Visual disturbance	70 (72.9)	54 (61.4)	0.130
Hearing disturbance	8 (8.3)	11 (12.5)	0.493
APACHE II score	13.7±7.0	15.3±6.4	0.534
Incidence of delirium	69 (71.9)	61 (69.3)	0.750

Values are presented as number (%) or mean±standard deviation.
APACHE: Acute Physiology and Chronic Health Evaluation.

gathered through nursing records, while the history of sleep disorders and the use of sleeping pills were collected through medical records to determine whether patients had a prior history of treatment before admission to the SICU. Data from the pre-intervention period were collected retrospectively, while data from the post-intervention period were collected prospectively after obtaining IRB approval.

Statistical Analysis

All statistical analyses were performed using IBM SPSS 21.0 (IBM Corp.). The chi-square test and t-test were used to analyze the general characteristics and clinical outcomes of target groups. A two-sided P-value less than 0.05 was considered statistically significant.

RESULTS

Study Population and Characteristics

A total of 463 patients was admitted to the SICU during the study period. However, 271 patients were excluded based on the predefined criteria. We enrolled a total of 192 patients; 101 patients were in the pre-intervention (control) group without environmental interventions, and 91 patients were in the post-intervention (intervention) group with environmental intervention. During the study period, five patients in the pre-intervention group and three in the post-intervention group dropped out owing to sudden exacerbation of their general condition, with an RASS score of –4 or –5. The final analysis included 96 patients in the pre-intervention group and 88 in the post-intervention group. There were no significant differences between baseline measures of the two groups (Table 1). Of the final cohort, 69 (71.9%) patients in the pre-intervention group and 61 (69.3%) in the post-intervention group developed delirium (Figure 3). No significant differences were observed between the pre- and post-intervention groups in any general characteristics, including sex, age, severity, or ventilator use (Table 2).

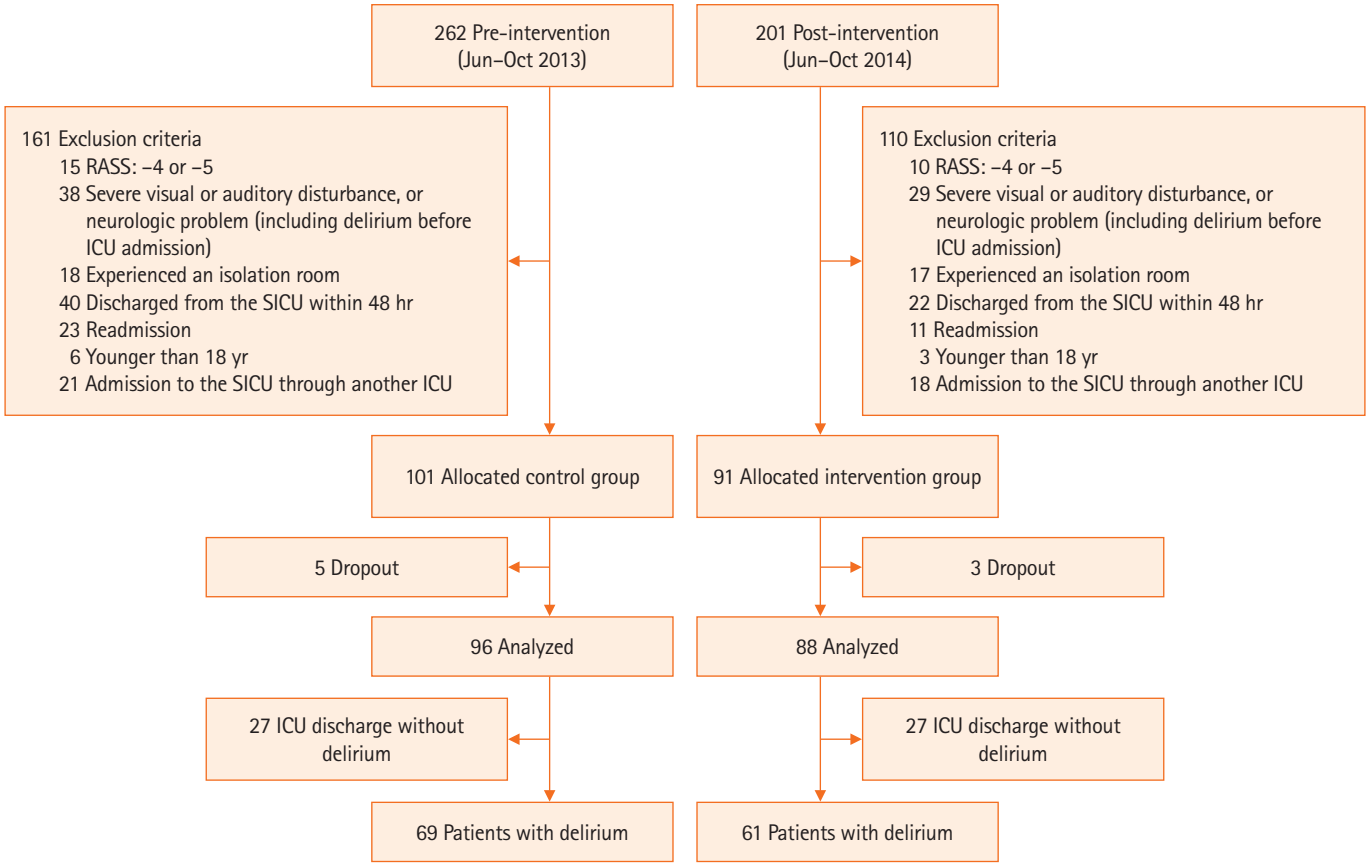

Figure 3. Flow diagram of study participants. RASS: Richmond Agitation-Sedation Scale; ICU: intensive care unit; SICU: surgical intensive care unit.

Clinical Outcomes before and after Environmental Interventions

No significant difference was observed between the pre- and post-intervention groups regarding the prevalence of patients who developed delirium (71.9% vs. 69.3%, P=0.75). No difference in the time of delirium onset was observed between the groups (2.6±2.4 days vs. 2.1±1.8 days, P=0.242). However, the duration of delirium was 14.4±19.1 days for patients in the pre-intervention group and 7.7±7.3 days for those in the post-intervention group, a significant reduction (P=0.027). Regarding secondary outcomes, the number of days of ventilator use tended to be lower for patients in the post- intervention group than for those in the pre-intervention group (15.3±22.9 days vs. 9.8±11.7 days, P=0.088). The LOS in the SICU was 20.0±22.9 days for patients in the pre-intervention group and 12.6±8.7 days for patients in the post-intervention group, a significant reduction (P=0.030). However, no significant differences in LOS in the general ward or the ICU or in the in-hospital or 6-month mortality rates were detected between the groups (Table 3).

DISCUSSION

The development of delirium predicts increases in the length of ICU and hospital stay, cost of care, and mortality. Therefore, many studies have aimed at preventing delirium. Our study revealed that environmental intervention could reduce the duration of delirium. We found that the mean duration of delirium after the environmental intervention was reduced from 14.4 to 7.7 days. As the duration of delirium decreased, the total number of days spent in the SICU decreased from 20.0 to 12.6 days. Pisani et al. [21] reported that longer durations of delirium resulted in higher 1-year mortality rates, with annual increases of 10%. In addition, Ely et al. [7] showed that delirium in ICU patients with mechanical ventilation is associated with increased 6-month mortality. Although our study did not detect any differences in mortality rates, shortening the duration of delirium could significantly reduce the days of ICU stay and the length

Table 2. General characteristics of delirium patients (n=130)

Characteristics	Pre-intervention (n=69)	Post-intervention (n=61)	P-value
Male	57 (82.6)	42 (68.9)	0.066
Age (yr)	67±11	67±14	0.934
>65 yr	44 (63.8)	43 (70.5)	0.416
Average sleep time (hr)	6.4±1.4	6.5±1.5	0.601
Sleep disorder	5 (7.2)	4 (6.6)	0.877
Use of sleeping pills	2 (2.9)	6 (9.8)	0.100
Visual disturbance	52 (75.4)	39 (63.9)	0.156
Hearing disturbance	7 (10.1)	7 (11.5)	0.807
Route of admission			0.152
Emergency room	32 (46.3)	26 (42.7)	
Operation room	29 (42.0)	27 (44.3)	
General ward	8 (11.7)	8 (13.1)	
Reason for admission			0.865
Postoperative monitoring	26 (37.7)	21 (34.4)	
Respiratory failure	18 (26.1)	16 (26.2)	
Sepsis	19 (27.5)	18 (29.5)	
Bleeding	2 (2.9)	3 (4.9)	
Others	4 (5.8)	3(4.9)	
APACHE II score	15.3±6.8	17.4±5.9	0.066
Mechanical ventilation	65 (94.2)	60 (98.4)	0.219
Use of restraint	65 (94.2)	58 (95.1)	0.825
Hemodialysis	12 (17.4)	7 (11.5)	0.341
Shock	35 (50.7)	36 (60.0)	0.291
Sedative drug	64 (92.8)	58 (95.1)	0.581
Use of benzodiazepine	16 (23.2)	9 (15.5)	0.279

Values are presented as number (%) or mean±standard deviation.
APACHE: Acute Physiology and Chronic Health Evaluation.

Table 3. Clinical outcomes pre- and post-intervention (n=130)

Characteristics	Pre-intervention (n=69)	Post-intervention (n=61)	P-value
Primary outcome			
Time of delirium onset (day)	2.6±2.4	2.1±1.8	0.242
Duration of delirium (day)	14.4±19.1	7.7±7.3	0.027
Secondary outcome			
Day of ventilator use	15.3±22.9	9.8±11.7	0.088
Length of ICU stay (day)	20.0±22.9	12.6±8.7	0.030
Length of GW stay (day)	25.9±32.9	29.7±41.1	0.561
Readmission to SICU	11 (15.9)	9 (14.7)	0.549
Length of hospital stay (day)	52.0±42.6	46.8±43.3	0.435
SICU mortality	8 (11.6)	9 (14.7)	0.257
In-hospital mortality	9 (13.0)	12 (19.7)	0.248
6-Month mortality	12 (17.4)	12 (19.7)	0.914

Values are presented as mean±standard deviation or number (%).
ICU: intensive care unit; GW: general ward; SICU: surgical intensive care unit.

of mechanical ventilation. Prolonged ICU stays can increase the risk of complications, including aspiration, pressure ulcers, ventilator-associated pneumonia, and post-intensive care syndrome [22]. As environmental intervention decreases ICU stay, it plays a crucial role in critical care.

Several studies have reported that the incidence of delirium can be reduced by environmental interventions that minimize the risk factors for delirium [5,6,23]. Vidán et al. [24] reported that non-pharmacologic interventions can reduce the incidence of delirium by 30%–40%. Similarly, in patients with a hip fracture, Björkelund et al. [25] documented a substantial reduction in the incidence of delirium (from 34% to 22%) with interventions such as hydration, oxygenation, analgesia, and optimization in the care environment. However, our results differ from those of other studies in a number of important aspects. In our study, the incidence of delirium was not significantly different before and after interventions. As with previous studies, for our patients, delirium developed within 2–3 days after SICU admission [3,26]. This short period was insufficient to observe the effect of environmental intervention on delirium onset. It is necessary to identify and minimize the risk factors associated with delirium onset, but there was a limitation in reducing incidence because most delirium occurred so soon after initial admission to the ICU.

Herein, the mean duration of delirium was 14 days, which is considerably longer than that reported in other studies (mean duration, 3–5 days) [3,27]. The duration of delirium depends on the severity of delirium and the composition of the ICU. In other studies, many patients were in the ICU for postoperative care after elective surgery; however, in our study, sepsis and respiratory failure patients accounted for most cases, which suggests that environmental intervention could substantially impact high-severity cases.

In addition to orientation and communication assistance, we focused on a proper sleep environment. Critically ill patients experience poor sleep, which worsens delirium. One study in the SICU found that patients only slept for 2 hours per day [28]. In the present study, a proper sleep environment was established by minimizing nonessential medical activities and providing earplugs and eye masks to be worn as desired. Before implementing the protocol, we performed radiography examinations, blood sampling, and weight measurements at night. After implementing the protocol, these tests were performed before sleep or in the morning to ensure a consistent sleep/wake cycle. However, there was no significant difference observed in the change in sleep duration between the pre-intervention and post-intervention groups. There was a limitation in appropriately assessing the quality of sleep. Future evaluation of sleep quality and additional analysis are necessary.

The main strength of our study is that specially trained nurses who were CAM-ICU educated examined the patients on every shift and verified delirium diagnoses three times per day. Early detection of delirium is an important factor in its treatment [17,29]. In previous reports, delirium was diagnosed once daily using the CAM-ICU or other diagnostic tools [3,27]. However, we performed the CAM-ICU thrice daily to improve the sensitivity of the delirium diagnosis; this increased sensitivity may positively affect the outcome of environmental interventions. Even before the intervention, delirium was evaluated using CAM-ICU, but the QI activities provided continuous education and increased validity and accuracy. Another strength of this study is that it was conducted only on critical ill surgical patients, who tend to have a high incidence of delirium. We prospectively analyzed the prevalence of delirium and the effectiveness of environmental interventions by comparing patients before and after intervention.

Nevertheless, there are some limitations to this study. First, use of the "before" and "after" design should be noted. No significant difference was observed between the characteristics of patients in the "before" and "after" groups. Second, our study was conducted at a single institution. As a relatively short-term study conducted within a single institution, it may have limitations in representing all critically ill patients. Additionally, the severity of the patients at our hospital may differ from those in other ICUs, making it challenging to generalize our findings. Also, the characteristics of the ICU, such as bed type being open-type or isolated-type, may have introduced bias. According to Zaal et al. [27], switching from an open-type ICU bed to a single-bed room can reduce the duration of delirium. Therefore, subgroup analysis may be required depending on the type of ICU bed. Finally, patient comorbidities may affect the occurrence of delirium and the LOS in the ICU, but correction for these confounding variables may not be sufficient. Future evaluation and additional analysis of risk factors related to delirium may be necessary.

Delirium is one of the main causes of prolonged ICU stay. Based on our findings, environmental intervention could be a useful tool for decreasing the duration of delirium in critically ill surgical patients. The tested environmental interventions are economical, safe, and effective. To implement an environmental intervention protocol, it is necessary to identify the risk factors of delirium and to introduce environmental changes

that can be realized and adapted to the actual circumstances of each hospital.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Methodology: HJL, YJJ, SKH. Data curation: NJC. Supervision: SKH. Writing–original draft: HJL, YJJ. Writing–review & editing: NJC, SKH.

REFERENCES

1. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. Am J Med 1994;97:278-88.
2. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 2009;5:210-20.
3. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg 2009;249:173-8.
4. Pisani MA, McNicoll L, Inouye SK. Cognitive impairment in the intensive care unit. Clin Chest Med 2003;24:727-37.
5. Holt R, Young J, Heseltine D. Effectiveness of a multi-component intervention to reduce delirium incidence in elderly care wards. Age Ageing 2013;42:721-7.
6. O'Hanlon S, O'Regan N, Maclullich AM, Cullen W, Dunne C, Exton C, et al. Improving delirium care through early intervention: from bench to bedside to boardroom. J Neurol Neurosurg Psychiatry 2014;85:207-13.
7. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-62.
8. Dammeyer JA, Mapili CD, Palleschi MT, Eagle S, Browning L, Heck K, et al. Nurse-led change: a statewide multidisciplinary collaboration targeting intensive care unit delirium. Crit Care Nurs Q 2012;35:2-14.
9. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
10. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852-7.
11. Arenson BG, MacDonald LA, Grocott HP, Hiebert BM, Arora RC. Effect of intensive care unit environment on in-hospital delirium after cardiac surgery. J Thorac Cardiovasc Surg 2013;146:172-8.
12. Serafim RB, Bozza FA, Soares M, do Brasil PE, Tura BR, Ely EW, et al. Pharmacologic prevention and treatment of delirium in intensive care patients: a systematic review. J Crit Care 2015;30:799-807.
13. Kang J, Lee M, Ko H, Kim S, Yun S, Jeong Y, et al. Effect of non-pharmacological interventions for the prevention of delirium in the intensive care unit: a systematic review and meta-analysis. J Crit Care 2018;48:372-84.
14. Patel J, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anaesthesia 2014;69:540-9.
15. Bounds M, Kram S, Speroni KG, Brice K, Luschinski MA, Harte S, et al. Effect of ABCDE bundle implementation on prevalence of delirium in intensive care unit patients. Am J Crit Care 2016;25:535-44.
16. Ali MA, Hashmi M, Ahmed W, Raza SA, Khan MF, Salim B. Incidence and risk factors of delirium in surgical intensive care unit. Trauma Surg Acute Care Open 2021;6:e000564.
17. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825-73.
18. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et

al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703-10.
19. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med 2004;32:2254-9.
20. Luetz A, Heymann A, Radtke FM, Chenitir C, Neuhaus U, Nachtigall I, et al. Different assessment tools for intensive care unit delirium: which score to use? Crit Care Med 2010;38:409-18.
21. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009;180:1092-7.
22. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. J Transl Int Med 2017;5:90-2.
23. Faustino TN, Suzart NA, Rabelo RN, Santos JL, Batista GS, Freitas YS, et al. Effectiveness of combined non-pharmacological interventions in the prevention of delirium in critically ill patients: a randomized clinical trial. J Crit Care 2022;68:114-20.
24. Vidán MT, Sánchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc 2009;57:2029-36.
25. Björkelund KB, Hommel A, Thorngren KG, Gustafson L, Larsson S, Lundberg D. Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study. Acta Anaesthesiol Scand 2010;54:678-88.
26. Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: an under-recognized syndrome of organ dysfunction. Semin Respir Crit Care Med 2001;22:115-26.
27. Zaal IJ, Spruyt CF, Peelen LM, van Eijk MM, Wientjes R, Schneider MM, et al. Intensive care unit environment may affect the course of delirium. Intensive Care Med 2013;39:481-8.
28. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. Br Med J (Clin Res Ed) 1985;290:1029-32.
29. Reade MC, Eastwood GM, Peck L, Bellomo R, Baldwin I. Routine use of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by bedside nurses may underdiagnose delirium. Crit Care Resusc 2011;13:217-24.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):488-497
https://doi.org/10.4266/acc.2023.00045

| pISSN 2586-6052 | eISSN 2586-6060

Implementation and effectiveness of a delirium care protocol in Thai critically ill children

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Background: Delirium in critically ill children can result in long-term morbidity. Our main objectives were to evaluate the effectiveness of a new protocol on the reduction, prevalence, and duration of delirium and to identify associated risk factors.

Methods: The effectiveness of the protocol was evaluated by a chart review in all critically ill children aged 1 month to 15 years during the study period. A Cornell Assessment of Pediatric Delirium score ≥9 was considered positive for delirium. Data on delirium prevalence and duration from the pre-implementation and post-implementation phases were compared. Univariate and multivariate analyses were used to identify the risk factors of delirium.

Results: A total of 120 children was analyzed (58 children in the pre-implementation group and 62 children in the post-implementation group). Fifty children (41.7%) screened positive for delirium. Age less than 2 years, delayed development, use of mechanical ventilation, and pediatric intensive care unit (PICU) stay >7 days were significantly associated with delirium. The proportion of children screened positive was not significantly different after the implementation (before, 39.7% vs. after, 43.5%; P=0.713). Subgroup analyses revealed a significant reduction in the duration of delirium in children with admission diagnosis of cardiovascular problems and after cardiothoracic surgery.

Conclusions: The newly implemented protocol was able to reduce the duration of delirium in children with admission diagnosis of cardiovascular problems and after cardiothoracic surgery. More studies should be conducted to reduce delirium to prevent long-term morbidity after PICU discharge.

Key Words: children; delirium; intensive care; morbidity

Original Article

Received: January 3, 2023
Revised: August 11, 2023
Accepted: October 7, 2023

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INTRODUCTION

Delirium is an acute cerebral dysfunction that can be caused by systemic illness or a medical treatment, especially in a critical care setting. It is sometimes referred to as intensive care unit psychosis or toxic psychosis [1,2]. According to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) in 2015, delirium is also defined as disturbances in consciousness, attention, perception, thinking, memory, emotion, and sleep-wake schedule [3]. The prevalence rate of delirium in critically ill children ranges

from 10% to 56%, with higher rates among children younger than 2 years [1-2,4-10].

Delirium can be classified into three subtypes: hyperactive, hypoactive, or mixed [1-2,11]. Children experiencing delirium have more frequent severe perceptual disturbances, mood lability, agitation, and visual hallucinations [11]. Critically ill children with delirium are associated with longer pediatric intensive care unit (PICU) and hospital stays, neurocognitive dysfunction, post-traumatic stress disorder, and higher rates of mortality [1,10]. Moreover, with a longer duration of delirium, more frequent severe cognitive and memory problems develop among children surviving critical illness [12,13]. Thus, delirium in critically ill children is a major health issue that can result in long-term morbidity.

Studies by Patel et al. in 2017 [14] and Jesus et al. [15] in 2020 suggested systematic approaches for the management of delirium in children who are critically ill. The first step of these approaches is to recognize and manage the underlying conditions and iatrogenic factors leading to delirium. Then, perform a stepwise approach using environmental modification, nonpharmacologic intervention, and then pharmacologic intervention [14,15]. A mnemonic known as "BRAIN MAPS" is used as a part of the assessment, evaluation, and treatment in the delirium clinical pathway and is recommended by the Society of Critical Care Medicine. BRAIN MAPS involves bringing oxygen (B), reducing or removing deliriogenic drugs such as benzodiazepines or anticholinergics (R), atmosphere modification (A), infection/inflammation control and reducing immobilization (I), treatment of new organ dysfunction and metabolic disturbances (NM), awakening schedule (A), pain (P), and sedation control (S) [16-18]. There is limited evidence of the effectiveness of such approaches in reducing delirium in critically ill children. Furthermore, there is no local guideline in Thailand on the management of delirium in critically ill children. Thus, the main objective of this study was to evaluate the effectiveness of the newly devised delirium care map protocol in the reduction of delirium in critically ill children in terms of both prevalence and duration, PICU stay, and ventilator days. The secondary objective was to identify the risk factors associated with delirium in critically ill children.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Thammasat University Hospital, Thammasat University, Thailand (No. MTU-EC-PE-0-246/65). Informed consent was waived due to the retrospective review of the implemented protocol.

KEY MESSAGES

- A total of 50 children (41.7%) screened positive for delirium.
- Age less than 2 years, delayed development, use of mechanical ventilation, and pediatric intensive care unit stay >7 days were significantly associated with delirium.
- The proportion of children with positive screening was not significantly different after the implementation (before, 39.7% vs. after, 43.5%; P=0.713).
- Subgroup analyses revealed a significant reduction in the duration of delirium in children with an admission diagnosis of cardiovascular problems and after cardiothoracic surgery.

Study Design and Participants

A chart review of all children aged 1 month to 15 years who were admitted to the PICU from March to October 2022 was conducted. Our PICU is a mixed medical-surgical tertiary, single-patient room intensive care unit that receives approximately 25–30 patients per month. The nurse-to-patient ratio is 1:1 or 1:2 based on the severity of the patient's condition.

Intervention

From March 2022, the Cornell Assessment of Pediatric Delirium (CAPD) has been used as a screening tool for delirium in our critical care unit. The CAPD was conducted in all patients admitted to the PICU every 8 hours at the start of the nursing shift. Before this, no screening tool for delirium was used in the unit. All pediatric critical care nurses were trained by attending pediatric intensivists and senior critical care nurses who were familiar with the screening tool. Good interrater reliability of 0.85 was obtained before initiation of the routine assessment. The CAPD is a valid screening tool with excellent sensitivity and specificity for critically ill children of all ages and can be conducted in patients with developmental delays. CAPD consists of eight questions aiming to assess consciousness, cognition, orientation, psychomotor activity, and affect/distress. The score was given on a Likert scale of 0–4 (0=always, 1=often, 2=sometimes, 3=rarely, and 4=never) based on the assessment. The CAPD is faster, needing less than 2 minutes to complete [1]. A CAPD score ≥9 is considered positive for delirium. Deeply sedated patients (Richmond Agitation-Sedation scale [RASS] <–4 or State Behavioral Scale [SBS] <–2) were not

assessed until awake. RASS is a 10-point scale for the evaluation of agitation and sedation ranging from +4 (combative) to −5 (unarousable) [19]. The SBS is also used for evaluation of sedation and agitation in mechanically ventilated children in our unit. This is a 6-point scale ranging from +2 (agitated) to −3 (unresponsive) [20]. These scales are currently used as a standard practice for evaluation of sedation and agitation in our PICU (RASS in non-mechanically ventilated children, SBS in mechanically ventilated children).

The delirium care map protocol based on the mnemonic "BRAIN MAPS" was outlined as a quality improvement project of the hospital by pediatric intensivists and pediatric critical care nurses in June 2022 to decrease the proportion and duration of patients with delirium (Figure 1). The components

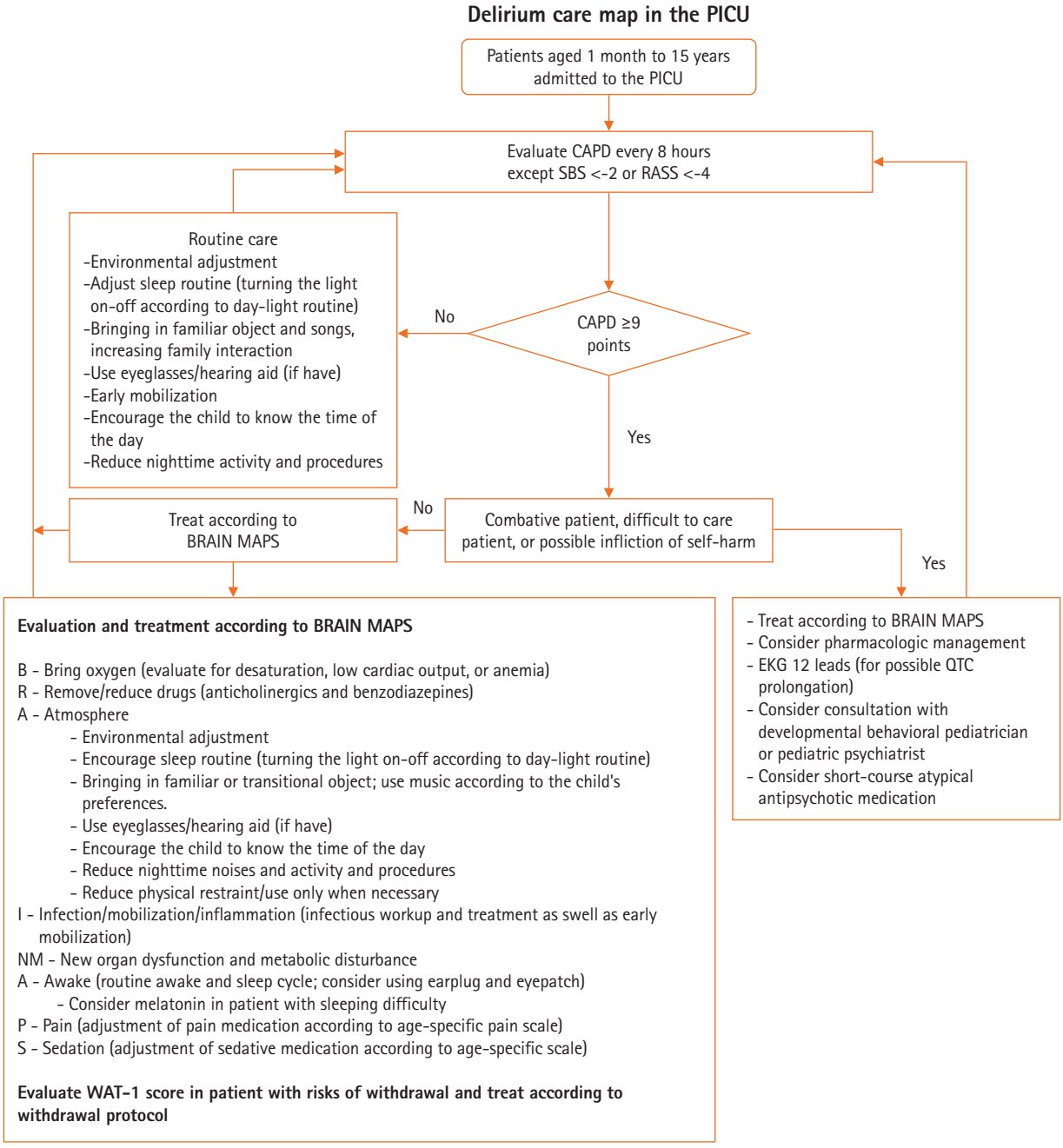

Figure 1. Protocol for delirium care of critically ill children. PICU: pediatric intensive care unit; SBS: State Behavioral Scale; RASS: Richmond Agitation-Sedation Scale; CAPD: Cornell Assessment of Pediatric Delirium; WAT-1: withdrawal assessment tool; EKG: electrocardiogram; QTC: corrected QT interval.

of the protocol mostly focus on the non-pharmacologic management of delirium, adjustment of the PICU environment, and treatment of the underlying conditions. Pharmacologic treatment of delirium was reserved only for patients who were combative or at risk of self-harm. A 1-month training period was required before implementation to ensure consistency and compliance with the protocol. Thus, the patients who were admitted from March 1, 2022, to June 30, 2022, were considered as a pre-implementation group, and the patients admitted from July 1, 2022, to October 31, 2022, served as the post-implementation group. To ensure the effectiveness of the protocol, screening and protocol compliance were randomly assessed. All demographic data, as well as admission diagnosis, underlying comorbidities, delirium duration, PICU duration, sedation, the neuromuscular blocking agent used, and ventilator days, were recorded.

Statistical Analyses

Delirium duration was calculated as the number of shifts with CAPD ≥9 points multiplied by 8 hours (shift duration). For instance, if a child screened positive for delirium 10 times during the PICU stay, the duration was recorded as 80 hours. Delayed development was defined using the red flags described by the American Academy of Pediatrics [21]. All demographic data, PICU length of stay, and ventilator days were analyzed using descriptive statistics. The prevalence of delirium was reported as a percentage. Data on delirium from the pre-implementation and post-implementation phases were compared with the expectation of reductions in delirium rates and duration. The Mann-Whitney U-test was used to compare quantitative data among intervention groups. Univariate analyses were used to identify the risk factors of delirium. Statistically significant factors from the univariate analyses were used for the adjustment during multivariate analyses. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS ver. 24 (IBM Corp.).

RESULTS

Demographic Data

The demographic data are presented in Table 1. A total of 120 children was admitted to the PICU during the study period. All children were included in the analysis. Fifty-eight children were allocated to the pre-implementation group and the remaining 62 children were allocated to the post-implementation group (Figure 2). The median age for the overall cohort was 3.1 years (interquartile range [IQR], 0.9–6.8), and 43 children (35.8%) were younger than 2 years. Approximately 56.7% of the participants were male.

Cardiovascular comorbidity served as the main underlying condition in the cohort (41.7%), followed by neurologic comorbidity (7.5%) and gastrointestinal comorbidity (5.8%). A total of 37 children (30.8%) had developmental delays and 56 children (46.7%) were admitted to the PICU for postoperative care. Among the children admitted for postoperative care, the major type of surgery was cardiothoracic surgery (32/56, 57%). The most common admission diagnoses were cardiovascular (38.2%) and gastrointestinal (13.3%) problems. The median Pediatric Risk for Mortality (PRISMI) III score [22] was 2.0 (IQR, 0.0–5.0). Inotropic medications were used in 47 children (39.2%) with a median vasoactive inotropic score (VIS) [23] of 14.0 (IQR, 7.0–24.0). Extracorporeal membrane oxygenator support (ECMO) was compulsory in four children (3.3%), one (1.7%) during the pre-implementation phase, and three (4.8%) in the post-implementation phase. A total of 48 children (40.0%) was mechanically ventilated with a median duration of 2.5 days (IQR, 1.0–8.8 days). Continuous infusion of sedatives and neuromuscular blocker (NMB) were used in 42 (35.0%) and nine (7.5%) children, respectively. Five children (4.2%) exhibited signs of withdrawal. The median PICU stay was 3.0 days (IQR, 1.0–8.0 days), and 35 children (29.2%) required PICU admission for greater than 7 days. Three children (2.5%) died during the study period. The overall demographic data including age, gender, underlying condition, admission diagnoses, developmental status, PRISM III score, VIS, ino-

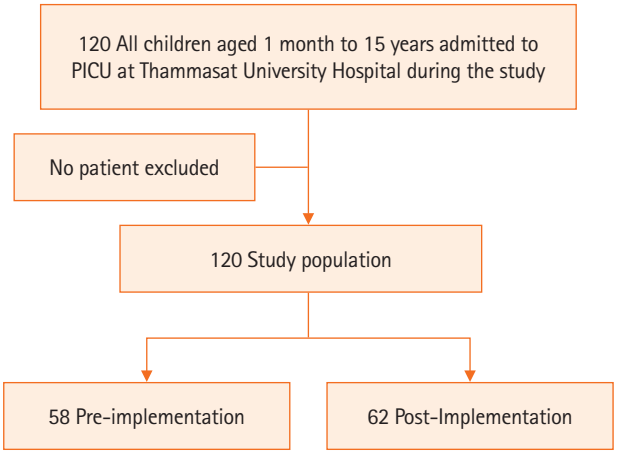

Figure 2. The flowchart for the study. All patients were followed until pediatric intensive care unit (PICU) discharge and were included for the final analysis.

Table 1. Demographic data among intervention groups

Factor	All patients (n=120)	Pre-intervention (n=58)	Post-intervention (n=62)	P-value
Median age (yr)	3.1 (0.9–6.8)	3.1 (0.9–5.0)	3.0 (0.6–7.8)	0.985
Age <2 yr	43 (35.8)	20 (34.5)	23 (37.1)	0.850
Male	68 (56.7)	33 (56.9)	35 (56.5)	1.000
Underlying disease				0.817
None	23 (19.2)	12 (20.7)	11 (17.8)	
Cardiovascular	50 (41.7)	22 (37.9)	28 (45.2)	
Neurologic	9 (7.5)	7 (12.1)	2 (3.2)	
Genetic	4 (3.3)	2 (3.4)	2 (3.2)	
Gastrointestinal	7 (5.8)	3 (5.2)	4 (6.5)	
Hematology and oncology	7 (5.8)	3 (5.2)	4 (6.5)	
Renal	2 (1.7)	1 (1.7)	1 (1.6)	
Pulmonology	5 (4.2)	2 (3.4)	3 (4.8)	
Trauma	1 (0.8)	1 (1.7)	-	
Allergy	7 (5.8)	5 (8.7)	2 (3.2)	
Endocrine	2 (1.7)	-	2 (3.2)	
Rheumatology	1 (0.8)	-	1 (1.6)	
Infectious disease	2 (1.7)	-	2 (3.2)	
Admission diagnosis				0.165
Cardiovascular	46 (38.2)	20 (34.6)	26 (41.9)	
Gastrointestinal	16 (13.3)	8 (13.8)	8 (12.9)	
Pulmonology	15 (12.5)	8 (13.8)	7 (11.3)	
Neurologic	12 (10.3)	7 (12.1)	5 (8.1)	
Asthmatic attack	10 (8.3)	9 (15.5)	1 (1.6)	
Renal	6 (5.0)	2 (3.4)	4 (6.5)	
Endocrine	6 (5.0)	1 (1.7)	5 (8.1)	
Septic shock	2 (1.7)	2 (3.4)	-	
Oncology	2 (1.7)	1 (1.7)	1 (1.6)	
Trauma	1 (0.8)	-	1 (1.6)	
Dental	1 (0.8)	-	1 (1.6)	
Genetic	1 (0.8)	-	1 (1.6)	
Orthopedics	1 (0.8)	-	1 (1.6)	
Rheumatology	1 (0.8)	-	1 (1.6)	
Delayed development	37 (30.8)	18 (31.0)	19 (30.6)	1.000
All-cause postoperative care	56 (46.7)	26 (44.8)	30 (48.4)	0.718
Median PRISM III	2.0 (0.0–5.0)	0.0 (0.0–5.0)	2.0 (0.0–7.0)	0.294
Median CAPD	7.0 (3.0–12.0)	7.0 (2.0–11.2)	7.0 (3.0–12.0)	0.874
Delirium	50 (41.7)	23 (39.7)	27 (43.5)	0.713
Delirium duration (hr)	40.0 (24.0–74.0)	56.0 (32.0–72.0)	32.0 (18.0–80.0)	0.274
Inotropes	47 (39.2)	21 (36.2)	26 (41.9)	0.577
Median vasoactive inotropic score [23]	14.0 (7.0–24.0)	16.0 (5.0–25.0)	13.0 (7.8–21.4)	0.192
ECMO support	4 (3.3)	1 (1.7)	3 (4.8)	0.619
Respiratory support				0.453
None	25 (20.8)	9 (15.5)	16 (25.8)	
Cannula	23 (19.2)	12 (20.7)	11 (17.7)	
HFNC	24 (20.0)	14 (24.1)	10 (16.1)	
MV	48 (40.0)	23 (39.7)	25 (40.3)	
Median MV days	2.5 (1.0–8.8)	3.0 (1.0–9.0)	2.0 (1.0–5.5)	1.000
MV >7 days	13/48 (27.1)	9/23 (39.1)	4/25 (16.0)	0.106
Sedation	42 (35.0)	19 (32.8)	23 (37.1)	0.703
Sedation >7 days	11/42 (26.2)	7/19 (36.8)	4/23 (17.4)	0.180
NMB	9 (7.5)	4 (6.9)	5 (8.1)	1.000
Withdrawal	5 (4.2)	3 (5.2)	2 (3.2)	0.672
Median PICU days	3.0 (1.0–8.0)	3.0 (1.0–7.2)	3.0 (1.0–8.0)	0.436
PICU >7 days	35 (29.2)	16 (27.6)	19 (30.6)	0.841
Mortality	3 (2.5)	1 (1.7)	2 (3.2)	1.000

Values are presented as median (interquartile range) or number (%).
PRISM: Pediatric Risk for Mortality [22]; CAPD: Cornell assessment for pediatric delirium; ECMO: extracorporeal membrane oxygenator; HFNC: high-flow nasal cannula; MV: mechanical ventilation; NMB: neuromuscular blocker; PICU: pediatric intensive care unit.

tropic support, ECMO support, respiratory support, sedation use, NMB use, and withdrawal were not significantly different between intervention groups.

Outcomes of Delirium Care Protocol

The compliance rate of the screening was 95%. The bundle compliance was randomly examined and found to be 70%. The most difficult components with which to comply were a sleeping routine and reduction of night-time noises. Parental visits were limited to 30 minutes each day to comply with the hospital policy. A total of 50 children (41.7%) had positive delirium screening. The median CAPD score for the overall cohort was 7.0 (3.0–12.0). The proportion of children with positive CAPD screening was not significantly different among groups (39.7% during the pre-intervention phase vs. 43.5% during the post-intervention phase; P=0.713). The median delirium duration during the post-intervention phase seemed to be shorter than the pre-intervention phase, but the difference was not significant (32.0 hours [IQR, 18.0–8.0] vs. 56.0 hours [IQR, 32.0–72.0], P=0.274). No children received atypical antipsychotics during the study period. The median CAPD score, mechanical ventilator support days, PICU stays, and mortality rates were not statistically different between the groups (Table 1).

In a subgroup analysis of children with the admission diagnosis of cardiovascular problems, there was a significant reduction in the duration of delirium after implementation of the protocol, from 64.0 hours (IQR, 54–80 hours) to 32.0 hours (IQR, 22–68 hours) (P=0.001). A similar result was found in children after cardiothoracic surgery (60.0 hours [IQR, 50–70] vs. 28.0 hours [IQR, 24–58], P=0.02).

Factors Associated with Positive Delirium Screening

Table 2 outlines the factors associated with delirium among participants. The proportion of children younger than 2 years was significantly higher in the positive delirium screening group (48.0% vs. 27.1%, P=0.022). There was also a significantly larger proportion of children with delayed development in the delirium group (52.0% vs. 15.7%, P<0.001). Children with positive screening for delirium had significantly higher median PRISM III scores, median CAPD scores, longer mechanical ventilation support days, and longer PICU stays. All children who required ECMO and NMB had positive delirium screening. Withdrawal was only found in children with delirium. The proportions of children with admission diagnosis of cardiovascular problems, who required mechanical ventilation, contin-

Table 2. Associating factors for positive delirium screening

Factor	Delirium (n=50)	No delirium (n=70)	P-value
Median age (yr)	2.2 (0.8–6.5)	3.6 (1.4–8.0)	0.115
Age <2 yr	24 (48.0)	19 (27.1)	0.022
Male	29 (58.0)	39 (55.7)	0.853
Underlying disease			0.819
None	9 (18.0)	14 (20.0)	
Cardiovascular	28 (56.0)	22 (31.5)	
Neurologic	3 (6.0)	6 (8.6)	
Genetic	2 (4.0)	2 (2.9)	
Gastrointestinal	-	7 (10.0)	
Hematology and oncology	2 (4.0)	5 (7.1)	
Renal	1 (2.0)	1 (1.4)	
Pulmonology	2 (4.0)	3 (4.3)	
Trauma	-	1 (1.4)	
Allergy	2 (4.0)	5 (7.1)	
Endocrine	-	2 (2.9)	
Rheumatology	-	1 (1.4)	
Infectious disease	1 (2.0)	1 (1.4)	
Admission diagnosis			0.026
Cardiovascular	28 (56.0)	18 (25.8)	
Gastrointestinal	2 (4.0)	14 (20.0)	
Pulmonology	8 (16.0)	7 (10.0)	
Neurologic	4 (8.0)	8 (11.5)	
Asthmatic attack	1 (2.0)	9 (12.9)	
Renal	2 (4.0)	4 (5.7)	
Endocrine	1 (2.0)	5 (7.1)	
Septic shock	1 (2.0)	1 (1.4)	
Oncology	1 (2.0)	1 (1.4)	
Trauma	1 (2.0)	-	
Dental	-	1 (1.4)	
Genetic	1 (2.0)	-	
Orthopedics	-	1 (1.4)	
Rheumatology	-	1 (1.4)	
Delayed development	26 (52.0)	11 (15.7)	<0.001
All-cause postoperative care	23 (46.0)	33 (47.1)	1.000
PRISM III	3.0 (0–7.2)	0 (0–4.0)	0.006
CAPD	12.5 (11.0–17.0)	3.0 (0–5.2)	<0.001
Inotropes	29 (58.0)	18 (25.7)	0.001
Vasoactive inotropic score [23]	14.0 (8.0–25.0)	14.5 (5.0–21.4)	0.853
ECMO support	4 (8.0)	-	0.028
Respiratory support			<0.001
None	6 (12.0)	19 (27.1)	
Cannula	4 (8.0)	19 (27.1)	
HFNC	7 (14.0)	17 (24.3)	
MV	33 (66.0)	15 (21.5)	
MV duration	5.0 (2.0–9.0)	1.0 (1.0–1.5)	0.013
MV >7 days	12/33 (36.4)	1/15 (6.7)	0.040
Sedation	29 (58.0)	13 (18.6)	<0.001
Sedation >7 days	10/29 (34.5)	1/13 (7.7)	0.127
Neuromuscular blocker	9 (18.0)	-	<0.001
Withdrawal	5 (10.0)	-	0.011
Median PICU stay	7.5 (3.0–13.0)	2.0 (1.0–4.0)	<0.001
PICU >7 days	28 (56.0)	7 (10.0)	<0.001
Mortality	1 (2.0)	2 (2.7)	1.000

Values are presented as median (interquartile range) or number (%).
PRISM: Pediatric Risk for Mortality [22]; CAPD: Cornell assessment for pediatric delirium; ECMO: extracorporeal membrane oxygenator; HFNC: high-flow nasal cannula; MV: mechanical ventilation; PICU: pediatric intensive care unit.

Table 3. Univariate analyses for associating factors of positive delirium screening

Factor	Crude odds ratio (95% CI)	P-value
Age <2 yr	2.48 (1.15–5.32)	0.022
Male	1.10 (0.53–2.28)	0.853
Presence of UD	1.14 (0.45–2.88)	0.819
All-cause postoperative care	0.96 (0.46–1.98)	1.000
Cardiovascular admission diagnosis	3.61 (1.66–7.83)	0.001
Delayed development	5.81 (2.48–13.59)	<0.001
Inotropic support	3.99 (1.84–8.67)	0.001
MV	7.12 (3.14–16.12)	<0.001
Prolonged MV >7 days	8.00 (0.93–68.62)	0.040
Sedation	6.06 (2.66–13.80)	<0.001
Prolonged sedation >7 days	6.32 (0.72–55.81)	0.127
Neuromuscular blocker	32.28 (1.83–569.05)	<0.001
Prolonged PICU stay >7 days	11.46 (4.39–29.91)	<0.001

CI: confidence interval; UD: underlying disease; MV: mechanical ventilation; PICU: pediatric intensive care unit.

Table 4. Multivariate analyses for associating factors of positive delirium screening

Factor	Adjusted odds ratio (95% CI)	P-value
Age <2 yr	3.41 (1.19–9.73)	0.014
Cardiovascular admission diagnosis	2.92 (0.78–10.91)	0.112
Delayed development	5.03 (1.73–14.59)	0.004
Inotropic support	0.26 (0.05–1.36)	0.112
MV	4.32 (0.47–40.12)	0.197
Prolonged MV >7 days[a)]	-	-
Sedation	2.05 (0.18–23.75)	0.565
Prolonged sedation >7 days	-	-
Neuromuscular blocker[a)]	-	-
Prolonged PICU stay >7 days	11.58 (2.90–46.23)	0.001

Adjusted for age <2 years, inotropic support, MV, prolonged PICU stay, and sedation.
CI: confidence interval; MV: mechanical ventilation; PICU: pediatric intensive care unit; UD: underlying disease.
a) Prolonged MV and neuromuscular blocker were not used for the final adjustment due to inadequate cells for the non-delirium group.

uous infusion of sedation, PICU stay >7 days, and mechanical ventilation >7 days were significantly larger in the delirium group. Median age, sex, underlying comorbidity, postoperative status, and mortality were not significantly different among groups.

The univariate and multivariate analyses of associating factors are presented in Tables 3 and 4. Age younger than 2 years, delayed development, admission diagnosis of cardiovascular problem, inotropic support, mechanical ventilator, mechanical ventilation >7 days, use of sedation and NMB, and PICU stay >7 days were associated with positive delirium screening (P<0.05) according to univariate analyses. After adjustment for significant factors, age younger than 2 years, delayed development, and PICU stay >7 days were associated with positive delirium screening with adjusted odds ratio (aOR) of 3.41 (95% confidence interval [CI], 1.19–9.73), 5.03 (95% CI, 1.73–14.59), and 11.58 (95% CI, 2.90–46.23), respectively.

DISCUSSION

The prevalence rate of delirium in this cohort was substantially high at 41.7%. This was comparable to previous studies, with the prevalence of delirium ranging from 10% to 57% [1,2,4-10]. We also demonstrated that age less than 2 years, delayed development, use of mechanical ventilation, and a PICU stay >7 days were significantly associated with delirium in critically ill children. These findings were consistent with the previously reported studies by Silver et al. [5] and Traube et al. [1].

A large study in critically ill adults revealed that the multimodal ABCDEF bundle was associated with a lower likelihood of delirium with an aOR of 0.60 (95% CI, 0.49–0.72) [24]. There were limited data on the effectiveness of the multimodal protocol for the management of delirium in critically ill children [25-27]. The implementation of our new delirium protocol was unable to significantly reduce the prevalence and duration of delirium in the overall study cohort. Nevertheless, in the subgroup analysis of children with the admission diagnosis of cardiovascular problems, there was a significant decline in the duration of delirium from 64.0 hours (IQR, 54–80 hours) to 32 hours (IQR, 22–68 hours) (P=0.001). The same was found in children after cardiothoracic surgery (60.0 hours [IQR, 50–70 hours] vs. 28.0 hours [IQR, 24–58 hours], P=0.02). Several studies have demonstrated that young children are among the most vulnerable groups to develop delirium during critical illness, especially after cardiothoracic surgery [28,29]. Similar findings were demonstrated in a recent study by Michel et al. [25], outlining a non-significant reduction of delirium prevalence after implementation of the delirium bundles but a significant reduction among children after cardiothoracic surgery. Unlike in our study, Michel et al. [25] showed a significant reduction of delirium in subgroups of children younger than 5 years. We were only able to illustrate a reduction in the duration of delirium in children with an admission diagnosis of cardiovascular problems and those after cardiothoracic

surgery. This might be due to the complex environment in the PICU setting and the multifactorial etiologies of delirium. Nevertheless, a reduction in the duration of delirium could alleviate the possible cognitive and memory problems after PICU discharge [12,13].

A prolonged stay in the PICU with the use of sedation and mechanical ventilation was associated with the development of delirium [1,5]. Approximately 29.2% of children in our cohort required a PICU stay >7 days, 40% required mechanical ventilation, and 35% required continuous infusion of sedation. Furthermore, children with positive screening for delirium had significantly higher median PRISM III scores, signifying the higher severity and complexity of the conditions. These factors might lead to continuous exposure of factors leading to delirium. Another factor limiting the effectiveness of the delirium protocol might be the pre-existing early mobilization protocol within the unit. A study by Simone et al. [27] showed that sequential implementation of delirium, sedation, and early mobility protocol can reduce the prevalence of delirium. An early mobilization protocol was implemented at our center in June 2020, and might have obscured the magnitude of the overall protocol effectiveness.

This study was one of the first aiming to reduce the prevalence of delirium in critically ill children by implementing the delirium care map protocol. A major strength of this study was that the compliance rate of the screening was as high as 95%. Furthermore, the compliance rate of the patients randomly examined every month was also high at approximately 70%. This compliance rate was comparable with the study by Michel et al. [25] (compliance screening rate of 95% and bundle adherence rate of 72%) and significantly higher than the study by Franken et al. [26] (compliance screening rate of 9%; no report on the compliance rate of the protocol). With the high compliance rate in both screening and protocol adherence, the true effectiveness of the protocol could be evaluated. Nonetheless, the most difficult protocol components to comply with were the reduction of night-time noises and encouragement of a sleep routine. Due to the nature of the university hospital, night-time admission and procedures as well as noises were difficult to control, regardless of the single-room patient status, which might compromise the effectiveness of the protocol. Furthermore, the limited time for a parental visit might also play a role in a non-significant change in the prevalence of delirium.

The other limitations of this study should also be outlined. This was a single-center study in a tertiary care university hospital. Thus, it might not be generalized to all hospital settings. A limited sample size within this cohort made it difficult to perform a subgroup analysis in different groups of children with different conditions. Nevertheless, this sample size was adequately powered for a reduction in the prevalence of delirium by 20% with β error of 0.2 and alpha error of 0.05. Regardless of these limitations, this is a pilot study for larger multicenter studies. More studies, especially multicenter studies, are also warranted to evaluate long-term cognitive decline and memory problems in children with delirium, as well as the validation and long-term effectiveness of the protocol.

Delirium is substantially prevalent among critically ill children in our cohort. The newly implemented protocol was able to reduce the duration of delirium in children with an admission diagnosis of cardiovascular problems and children after cardiothoracic surgery. More studies should be conducted to reduce delirium and prevent long-term morbidity in critically ill children after PICU discharge.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

This study was supported by the Research Group in Pediatric Care of the Faculty of Medicine, Thammasat University.

ACKNOWLEDGMENTS

The authors would like to show appreciation to all the residents, faculty, and nursing staff of our hospital as well as the Research Group for Pediatric Care of the Faculty of Medicine, Thammasat University for their strong support and extensive cooperation in making this project successful.

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ministration: all authors. Funding acquisition: CC. Writing–original draft: all authors. Writing–review & editing: all authors.

REFERENCES

1. Traube C, Silver G, Kearney J, Patel A, Atkinson TM, Yoon MJ, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU. Crit Care Med 2014;42:656-63.
2. Shieveld JN, Ista E, Knoester H, Molag ML. Pediatric delirium: a practical approach. In Rey JM, editor. IACAPAP e-textbook of child and adolescent mental health. International Association for Child and Adolescent Psychiatry and Allied Professions; 2015. p. 1-16.
3. World Health Organization. International statistical classification of diseases and related health problems 10th revision (ICD-10) [Internet]. World Health Organization; 2015 [cited 2023 Aug 20]. Available from: https://icd.who.int/browse10/2015/en#/F00-F09
4. Ista E, van Beusekom B, van Rosmalen J, Kneyber MC, Lemson J, Brouwers A, et al. Validation of the SOS-PD scale for assessment of pediatric delirium: a multicenter study. Crit Care 2018;22:309.
5. Silver G, Traube C, Gerber LM, Sun X, Kearney J, Patel A, et al. Pediatric delirium and associated risk factors: a single-center prospective observational study. Pediatr Crit Care Med 2015;16:303-9.
6. Silver G, Traube C, Kearney J, Kelly D, Yoon MJ, Nash Moyal W, et al. Detecting pediatric delirium: development of a rapid observational assessment tool. Intensive Care Med 2012;38:1025-31.
7. Traube C, Silver G, Reeder RW, Doyle H, Hegel E, Wolfe HA, et al. Delirium in critically ill children: an international point prevalence study. Crit Care Med 2017;45:584-90.
8. Smith HA, Boyd J, Fuchs DC, Melvin K, Berry P, Shintani A, et al. Diagnosing delirium in critically ill children: validity and reliability of the Pediatric Confusion Assessment Method for the Intensive Care Unit. Crit Care Med 2011;39:150-7.
9. Smith HA, Gangopadhyay M, Goben CM, Jacobowski NL, Chestnut MH, Savage S, et al. The preschool confusion assessment method for the ICU: valid and reliable delirium monitoring for critically ill infants and children. Crit Care Med 2016;44:592-600.
10. Traube C, Silver G, Gerber LM, Kaur S, Mauer EA, Kerson A, et al. Delirium and mortality in critically ill children: epidemiology and outcomes of pediatric delirium. Crit Care Med 2017;45:891-8.
11. Leentjens AF, Schieveld JN, Leonard M, Lousberg R, Verhey FR, Meagher DJ. A comparison of the phenomenology of pediatric, adult, and geriatric delirium. J Psychosom Res 2008;64:219-23.
12. Tasker RC, Menon DK. Critical care and the brain. JAMA 2016;315:749-50.
13. Turkel SB. Pediatric delirium: recognition, management, and outcome. Curr Psychiatry Rep 2017;19:101.
14. Patel AK, Bell MJ, Traube C. Delirium in pediatric critical care. Pediatr Clin North Am 2017;64:1117-32.
15. Jesus AO, Jones L, Linares R, Buck ML, Frank DU. Management of hyperactive delirium in the pediatric intensive care unit: case series of three young children. J Pediatr Intensive Care 2020;9:119-23.
16. Smith HA, Berutti T, Brink E, Strohler B, Fuchs DC, Ely EW, et al. Pediatric critical care perceptions on analgesia, sedation, and delirium. Semin Respir Crit Care Med 2013;34:244-61.
17. Bettencourt A, Mullen JE. Delirium in children: identification, prevention, and management. Crit Care Nurse 2017;37:e9-18.
18. Smith HA, Besunder JB, Betters KA, Johnson PN, Srinivasan V, Stormorken A, et al. 2022 Society of Critical Care Medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. Pediatr Crit Care Med 2022;23:e74-110.
19. Kerson AG, DeMaria R, Mauer E, Joyce C, Gerber LM, Greenwald BM, et al. Validity of the Richmond Agitation-Sedation Scale (RASS) in critically ill children. J Intensive Care 2016;4:65.
20. Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med 2006;7:107-14.
21. Hagan JF, Shaw JS, Duncan PM. Bright futures: guidelines for health supervision of infants, children, and adolescents. 3rd ed. American Academy of Pediatrics; 2008.
22. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 1996;24:743-52.
23. Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-inotropic score: evolution, clinical utility, and pitfalls. J Cardiothorac Vasc Anesth 2021;35:3067-77.
24. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med 2019;47:3-14.
25. Michel J, Schepan E, Hofbeck M, Engel J, Simma A, Neunhoeffer F. Implementation of a delirium bundle for pediatric intensive care patients. Front Pediatr 2022;10:826259.

26. Franken A, Sebbens D, Mensik J. Pediatric delirium: early identification of barriers to optimize success of screening and prevention. J Pediatr Health Care 2019;33:228-33.
27. Simone S, Edwards S, Lardieri A, Walker LK, Graciano AL, Kishk OA, et al. Implementation of an ICU bundle: an interprofessional quality improvement project to enhance delirium management and monitor delirium prevalence in a single PICU. Pediatr Crit Care Med 2017;18:531-40.
28. Meyburg J, Dill ML, Traube C, Silver G, von Haken R. Patterns of postoperative delirium in children. Pediatr Crit Care Med 2017;18:128-33.
29. Semple D, Howlett MM, Strawbridge JD, Breatnach CV, Hayden JC. A systematic review and pooled prevalence of delirium in critically ill children. Crit Care Med 2022;50:317-28.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):498-506
https://doi.org/10.4266/acc.2023.01354

| pISSN 2586-6052 | eISSN 2586-6060

Eleven years of experience in operating a pediatric rapid response system at a children's hospital in South Korea

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Background: Various rapid response systems have been developed to detect clinical deterioration in patients. Few studies have evaluated single-parameter systems in children compared to scoring systems. Therefore, in this study we evaluated a single-parameter system called the acute response system (ARS).

Methods: This retrospective study was performed at a tertiary children's hospital. Patients under 18 years old admitted from January 2012 to August 2023 were enrolled. ARS parameters such as systolic blood pressure, heart rate, respiratory rate, oxygen saturation, and whether the ARS was activated were collected. We divided patients into two groups according to activation status and then compared the occurrence of critical events (cardiopulmonary resuscitation or unexpected intensive care unit admission). We evaluated the ability of ARS to predict critical events and calculated compliance. We also analyzed the correlation between each parameter that activates ARS and critical events.

Results: The critical events prediction performance of ARS has a specificity of 98.5%, a sensitivity of 24.0%, a negative predictive value of 99.6%, and a positive predictive value of 8.1%. The compliance rate was 15.6%. Statistically significant increases in the risk of critical events were observed for all abnormal criteria except low heart rate. There was no significant difference in the incidence of critical events.

Conclusions: ARS, a single parameter system, had good specificity and negative predictive value for predicting critical events; however, sensitivity and positive predictive value were not good, and medical staff compliance was poor.

Key Words: cardiac arrest; early warning score; hospital rapid response team; intensive care units; pediatrics

Original Article

Received: October 27, 2023
Revised: October 31, 2023
Accepted: October 31, 2023

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INTRODUCTION

It is imperative to identify patient deterioration as early as possible to prevent significant delays in diagnosis and treatment that might result in life-threatening consequences such as cardiac arrest, unanticipated intensive care unit (ICU) admission, and even death [1-5]. Thus, an increasing number of hospitals have implemented a rapid response system (RRS) to

detect early warning signs from patients and use preemptive measures to prevent major adverse events from occurring [6].

An RRS consists of two components: the afferent component, which is for early recognition of clinical deterioration in a patient, and the efferent component, which is the process of timely therapeutic intervention [7]. The afferent component of RRS can be largely divided into two different types based on its triggering method: a single-parameter-based activation and a scoring system-based activation [8,9]. A single-parameter system is activated when at least one parameter exceeds a predefined threshold. This system is generally easier to implement in hospitals because it only requires a certain number of simple criteria to be defined. However, alarm fatigue could be a potential problem when a single-parameter system is used because even a single value out of its normal range can trigger the RRS, potentially causing an unnecessarily large volume of false-positive activations [10-14]. In contrast, RRS activation through a scoring system is dependent upon an accumulation of scores that reflect the severity of the physiological abnormalities, and it is triggered only when it exceeds a certain score. This type of system avoids the high false-positive activation rate of the single-parameter system because it uses not only one parameter but a sum of scores from various parameters to be activated. However, scoring-based systems are more complicated than single-parameter systems; they are more difficult to implement and operate in most hospitals [15-19].

The efficacy of the RRS for the two different activation types has long been a topic of debate, but mostly in adult studies. Only a few pediatric studies on pediatric RRS can be found, and most of those focus only on the scoring-based RRS, commonly referred to as the pediatric early warning system (PEWS). Notably, a large-scale randomized clinical trial was conducted in Canada in 2015, and a comprehensive review of 66 studies with 27 unique identification tools was performed in the United Kingdom in 2019 to assess the effectiveness and validity of PEWS [5,8]. A few additional prospective studies estimated the sensitivity of RRS, but they were all based on different types of PEWS [16-18]. Reports on single-parameter RRS, especially for the pediatric population, are scarce. One Korean study used a single variable, which was heart rate (HR) [6], and another Korean study used changes in HR and respiratory rate (RR) as variables for their RRS [20]. They were both small-scale, single-center retrospective studies that are designed to evaluate the efficacy of the single-parameter RRS itself. Therefore, they were not representative of comprehensive evaluations of RRS activation based on a single-parameter system [6,20].

KEY MESSAGES

- The single-parameter acute reactive system has good negative predictive ability for the occurrence of critical events but has low positive predictive ability.
- There was no significant difference in the frequency of critical events based on whether acute response system (ARS) was activated.
- Development of trigger tools for improving the predictive ability of ARS is necessary, and there is a need for sufficient infrastructure in the intensive care unit to care for clinical deterioration that is not detected in advance.

Therefore, as the institution that pioneered the Korean RRS both in adults and children, 11 years ago, we conducted a comprehensive evaluation including predictive performance for single-parameter-based RRS in children. Despite the retrospective nature of this study, our accumulated data and over ten years of experience will enable us to reach a meaningful conclusion.

MATERIALS AND METHODS

Ethics Statement

This study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (No. H-1904-161-1031). Informed consent was waived because of the retrospective nature of the study.

Study Setting and the RRS

This retrospective observational study was conducted at a single tertiary children's hospital with 350 beds. Patients under the age of 18 years who were admitted to the general ward from January 2012 to August 2023 were included. In this children's hospital, the single-parameter RRS was developed and implemented since 2010 under the name acute response system (ARS). Based on the system developed by Tibball et al. [2] in 2005 [6], thresholds by age group for each of the following seven parameters were set: systolic blood pressure (SBP), HR, RR, oxygen saturation measured by pulse oxygen saturation (SpO_2), decreased perfusion, change in mentality, and urine output. The RRS was activated when at least one of the parameters exceeded the threshold. After ARS activation, a decision to either maintain or deactivate was made when a patient's

condition improved or when the patient was admitted to the pediatric ICU (PICU). The ARS thresholds by age group are shown in Table 1.

Data Collection and Preprocessing

The data set used in the analysis was provided by the data warehouse of the hospital information system. A patient's age, sex, SBP, diastolic blood pressure, HR, RR, body temperature (BT), and SpO_2 were measured during hospitalization, and the time of vital sign measurement along with the location of the patient were recorded. Vital signs measured outside of general wards, such as operating rooms or ICUs, were excluded from the analysis. The collected vital signs that fell into the category of non-physiologic range were excluded from the analysis because of the possibility of keystroke errors in the process of inputting the value of vital signs. Non-physiologic range was defined as follows: HR >300 beats/min or <30 beats/min, RR >120 breaths/min or <5 breaths/min, SBP >300 mm Hg or <30 mm Hg, and BT >42 °C or <30 °C. Cases where vital sign values were recorded as strings or ranges rather than numbers were also excluded from the analysis.

Outcomes

The primary outcome of this study was to evaluate the performance of the ARS, which is defined as the predictive power of critical events. A critical event was defined as an unexpected PICU transfer or cardiopulmonary resuscitation (CPR) occurrence in a general ward. Unexpected PICU transfer was defined as PICU admission due to an acutely worsening clinical condition, excluding PICU admission for routinely planned postoperative care or planned procedures. A positive prediction of the ARS was defined as a case where a critical event occurred within 48 hours after the ARS was activated.

The secondary outcomes were compliance of the medical staff in activating the ARS, degree of contribution of each parameter to ARS activation, correlation between parameters and the occurrence of actual critical events, and the frequency of critical events by year. Compliance for ARS activation was evaluated by calculating the cases where ARS was not activated when it was required. In cases where compliance was low, we also analyzed the performance of predicting critical events when compliance was assumed to be 100%.

Statistical Analyses

To evaluate the critical event prediction performance of the ARS, all vital sign measurements were divided into an activation group and a non-activation group depending on the actual activation status of the ARS. The occurrence of critical events was compared for each group. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were analyzed for this evaluation.

Identifying the instances where ARS should have been activated—in other words, missed ARS activation—is necessary to calculate the degree of compliance with ARS. Among the seven parameters for ARS activation, SBP, HR, RR, and SpO_2 are parameters that can be collected from past medical records. However, parameters such as perfusion, mental change, and urine output reduction are not easy to collect retrospectively. Thus, we evaluated missed ARS activation cases using only the four reliably available parameters (SBP, HR, RR, and SpO_2). Possible underestimation due to the utilization of only four parameters in identifying missed ARS activation cases may be an important consideration during interpretation. Additionally, patients with underlying heart disease may have a baseline SpO_2 at rest lower than that of normal children, opening the possibility that the recorded SpO_2 value alone will not accurately reflect compliance of the ARS activation. Therefore, patients with underlying heart disease were excluded from the compliance analysis.

To analyze the relevance between critical events and triggered parameters, the following subgroups were created based on the activation criteria of each parameter: low SBP group,

Table 1. ARS activation criteria by parameter and age group

Age group	HR (beats/min)	RR (breaths/min)	SBP (mm Hg)	SpO_2 (%)	Decreased perfusion	Mental change	Urine output (ml/kg/hr)
<3 mo	<100 or >180	<25 or >60	<60	<90	Yes	Changed	<1
4–<24 mo	<100 or >180	<20 or >50	<70				<1
2–<5 yr	<90 or >150	<15 or >40	<75				<0.5
5–<10 yr	<80 or >140	<15 or >35	<80				<0.5
≥10 yr	<60 or >130	<13 or >35	<90				<0.5

ARS: acute response system; HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure; SpO_2: pulse oxygen saturation.

low HR group, high HR group, low RR group, high RR group, and low SpO_2 group. Logistic regression analysis was used to analyze the association of critical events within each group. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Categorical and continuous variables are presented as numbers (%) and medians (interquartile range), respectively. Data preprocessing and statistical analyses were performed using R software version 4.3.0 (R Foundation for Statistical Computing). P-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

During the study period, 94,219 patients were admitted 177,077 times, and a total of 20,493,885 vital signs were measured. After applying the exclusion criteria, 7,663,326 vital sign measurements were included in the analyses (Figure 1). Patient age was 5 years (interquartile range, 1–11 years), and 58.1% were boys. Other baseline characteristics of each group are summarized in Table 2.

Main Outcomes

The positive predictive power of the ARS for predicting critical events was excellent, with a specificity of 98.5% and an NPV of 99.6%. However, the sensitivity and PPV of the ARS were low, at 24.0% and 8.1%, respectively (Figure 2A). The compliance rate of ARS activation was 15.6%, which was very poor (Figure 2B). When the positive predictions were calculated with the assumption of 100% compliance, the NPV came out to be 99.6%, which is the same as for low compliance. Sensitivity, on the other hand, increased significantly, from 26.8% to 88.5%, while the specificity decreased from 98.5% to 38.5%, and the PPV decreased from 8.1% to 1.8% (Figure 2A and C). A subgroup analysis was performed to evaluate the association between occurrence of critical events and characteristics of ARS parameters. Univariable and multivariable logistic regression analyses showed that the occurrence of critical events significantly increased in most groups (low SBP group, high HR group, low RR group, high RR group, and low SpO_2 group). However, the low HR group showed a significant decrease in the occurrence of critical events (Table 3).

The incidences of CPR events and unexpected PICU admissions per 1,000 patient-days were 1.84 and 0.13, respectively. The annual incidences of CPR events and unexpected PICU admissions per 1,000 patient-days in the activated ARS group were 0.069 and 0.871, respectively, while in the non-activated ARS group, these rates were 0.063 and 0.965, respectively. There were 58 CPR events in the non-activated ARS group, with the highest occurrence (29.3%) in the cardiology ward and the cardiothoracic surgery ward. The frequency of CPR events in locations other than the general ward was significantly different, with eight CPR events in the non-activated ARS group and only one CPR event in the activated ARS group (Supplementary Table 1). There was no difference in the incidence of unexpected PICU admissions and CPR events between the non-activated ARS group and the activated ARS group. The reduction in occurrence of CPR events was higher in the activated ARS group, but the reduction in unexpected PICU admissions was higher in the non-activated ARS group. Meanwhile, unexpected PICU admissions showed minimal variation within the activated ARS group (Figure 3).

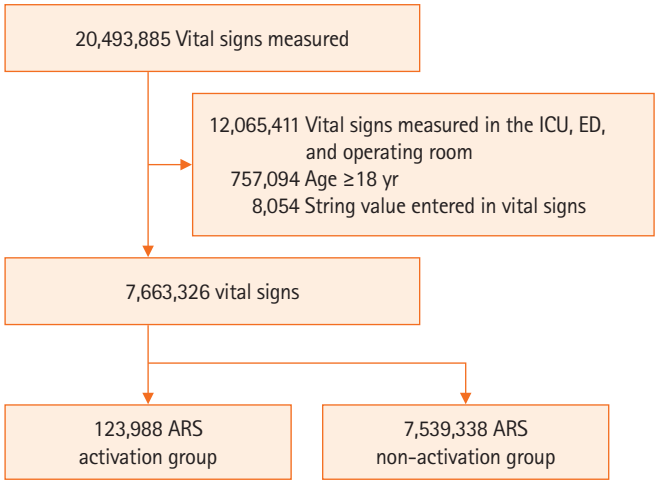

Figure 1. Flowchart of the study. The acute response system (ARS) activation group indicates that medical staff activated ARS during vital sign measurements, regardless of whether the criteria for ARS were met. The ARS non-activation group refers to cases where medical staff did not activate ARS during vital sign measurements, regardless of whether the criteria for ARS were met. ICU: intensive care unit; ED: emergency department.

DISCUSSION

In this study, we analyzed the performance of a pediatric single-parameter RRS in predicting critical events and clinical characteristics experienced during its activation. Prediction of critical events showed good specificity and NPV, while sensitivity and PPV were low. In operating the ARS, a single-parameter RRS, the authors expected that, because the system

Table 2. Characteristics of each group according to the ARS activation

Variable	Total (n=7,663,326)	ARS non-activation group (n=7,539,338)	ARS activation group (n=123,988)
Age (yr)	5 (1–11)	5 (1–11)	6 (2–10)
Age group			
0–<3 mo	474,630 (6.2)	470,387 (6.2)	4.243 (3.4)
3–<24 mo	1,669,518 (21.8)	1,645,913 (21.8)	23,274 (19.0)
2–<5 yr	1,325,109 (17.3)	1,298,835 (17.2)	26,274 (21.2)
5–<10 yar	1,754,663 (22.9)	1,718,786 (22.8)	35,877 (28.9)
≥10 yr	2,439,406 (31.8)	2,405,417 (31.9)	33,989 (27.4)
Male	4,454,132 (58.1)	4,381,075 (58.1)	73,057 (58.9)
Vital sign			
SBP (mm Hg)	104 (94–114)	104 (94–114)	103 (90–115)
DBP (mm Hg)	60 (51–70)	60 (51–70)	60 (50–72)
HR (beats/min)	108 (90–129)	108 (90–129)	118 (78–143)
RR (breaths/min)	24 (20–30)	24 (20–30)	32 (24–46)
SpO_2 (%)	100 (98–100)	100 (98–100)	98 (95–100)
BT (°C)	36.9 (36.5–37.3)	36.8 (36.5–37.3)	37.1 (36.6–37.8)
Abnormal ARS criteria			
Low HR	350,863 (4.6)	312,870 (4.1)	37,993 (30.6)
High HR	233,251 (3.0)	202,456 (2.7)	30,795 (24.8)
Low SBP	91,800 (1.2)	80,180 (1.1)	11,620 (9.4)
Low RR	10,451 (0.1)	8,206 (0.1)	2,245 (1.8)
High RR	105,918 (1.4)	64,727 (0.9)	41,191 (33.2)
Low SpO_2	161,371 (2.1)	149,619 (2.0)	11,752 (9.5)
Decreased perfusion	26 (0.0)	-	26 (0.0)
Decreased urination	0	-	0
Mental change	0	-	0
Ward[a)]			
Neurology	1,208,113 (15.8)	1,194,031 (15.8)	14,082 (11.4)
Cardiology	1,020,942 (13.3)	1,007,496 (13.4)	13,446 (10.8)
Gastroenterology	1,000,084 (13.1)	993,421 (13.2)	6,663 (5.4)
Nephrology/rheumatology	934,375 (12.2)	921,627 (12.2)	12,748 (10.3)
Hemato-oncology	1,027,024 (13.4)	980,969 (13.0)	46,055 (37.1)
Other pediatric diseases	965,845 (12.6)	938,405 (12.4)	27,440 (22.1)
Psychiatrics	87,178 (1.1)	87,171 (1.2)	7 (0.0)
Minor surgery	1,297,579 (16.9)	1,296,187 (17.2)	1,392 (1.1)
Other locations	122,186 (1.6)	120,031 (1.6)	2,155 (1.7)

Values are presented as median (interquartile range) or number (%).
ARS: acute response system; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; SpO_2: pulse oxygen saturation; BT: body temperature.
a) Each ward and its corresponding department are follows: Neurology - neurology department and neurosurgery; Cardiology - cardiology department and thoracic surgery; Gastroenterology - gastroenterology department and general surgery; Nephrology - nephrology department and urosurgery, Other pediatric diseases - endocrinology department, pulmonology department, and infection department; Minor surgery - orthopedics and ophthalmology; Other locations – radiology imaging unit, hemodialysis unit, endoscopy unit and etc.

was activated with only one anomaly, ARS activation could increase the alarm fatigue of the medical staff, especially when the patient's condition was not serious. Even if the workload of medical staff is high, this system was maintained with the idea that patients who are deteriorating should not be ignored, i.e., even if the PPV was low, the sensitivity was expected to remain high. However, PPV and sensitivity were low at 21.4%. There may be two reasons for low sensitivity. The first is that

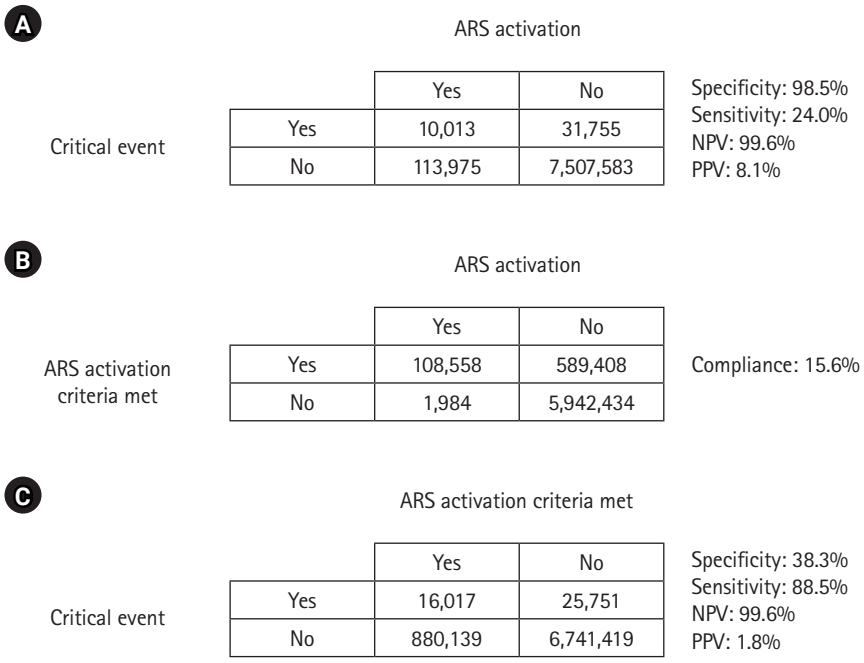

Figure 2. Effectiveness of the acute response system (ARS) and compliance with ARS activation. The ability to predict critical events by activating ARS in the real ward (A) and calculated compliance of the system (B). The ability of the ARS to predict critical events (C). Success in prediction is considered a critical event, defined as an unexpected pediatric intensive care unit admission or cardiopulmonary resuscitation event, occurring within 48 hours of ARS activation. NPV: negative predictive value; PPV: positive predictive value.

Table 3. Association between ARS activation criteria and actual critical event occurrence

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
HR group				
Normal	Reference		Reference	
Low	0.853 (0.808–0.900)	<0.001	0.593 (0.539–0.651)	<0.001
High	5.280 (5.129–5.435)	<0.001	4.592 (4.378–4.815)	<0.001
RR group				
Normal	Reference		Reference	
Low	4.051 (3.522–4.660)	<0.001	1.845 (1.550–2.195)	<0.001
High	14.398 (14.001–14.806)	<0.001	4.922 (4.734–5.117)	<0.001
SBP group				
Normal	Reference		Reference	
Low SBP	2.965 (2.811–3.127)	<0.001	2.558 (2.337–2.800)	<0.001
SpO_2 group				
Normal	Reference		Reference	
Low SpO_2	3.536 (3.420–3.656)	<0.001	1.354 (1.276–1.436)	<0.001

ARS: acute response system; OR: odd ratio; CI: confidence interval; HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure; SpO_2: pulse oxygen saturation.

the activation criteria are inadequate, and the other is that compliance for ARS activation is low. We think that the second reason is more important than the first because the NPV was high at 99.6%, and we believe this is supported by the fact that ARS activation compliance of the medical staff was very low at 15.6%.

The ARS is activated when an abnormal value for each parameter is measured: the nurse in charge enters the abnormal

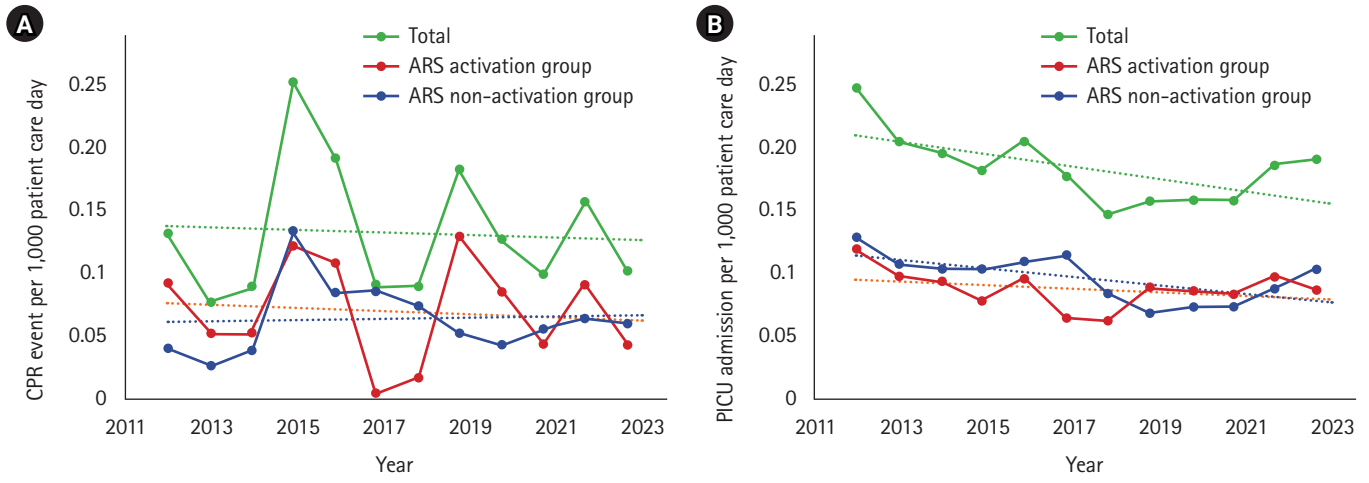

Figure 3. The annual changes in the number of critical events. The annual trends based on whether the acute response system (ARS) was activated within 48 hours of a critical event. Cardiopulmonary resuscitation (CPR) event (A) and unexpected pediatric intensive care unit (PICU) admission (B). ARS was divided into an ARS activation group and a non-activation group according to whether ARS was activated within 48 hours prior to the occurrence of critical events.

value into the medical record first, and the attending doctor confirms it. Therefore, low compliance is due to the structural fact that, even if there is an abnormal value that is outside the criteria, it cannot be activated unless the nurse or doctor in charge confirms it. Considering that the purpose of the ARS is to detect and intervene in a patient's deterioration at an early stage, it may be somewhat contradictory to require the primary care provider to confirm the ARS activation process. This is supported by the fact that when the ARS is simplified, which assumes 100% compliance with medical staff, the sensitivity increases dramatically (from 24.0% to 88.5%), even though the PPV becomes lower. The NPV remained unchanged at 99.6%, which is very high, suggesting that the medical staff's compliance with the application of single-parameter RRS may cause serious problems.

It is also interesting that the occurrence of critical events was significantly higher for abnormal parameters, whereas the occurrence of critical events was lower for HR below the criteria than for normal HR (Table 3). These results are consistent with a retrospective observational study in children that reported that RRS activation for bradycardia alone did not lead to adverse outcomes [6]. On the other hand, one adult study reported lower HR in the older age group compared with patients under 65 years old before cardiac arrest, suggesting that HR may be affected by other factors such as age as well as patient deterioration [21]. Even considering these results from the literature, it is difficult to fully explain how low HR was associated with lower occurrence of critical events than normal HR. Therefore, we think that it can be explained by the phenomenon of lower HR at rest, i.e., if the patient was not in a stressful situation, low HR may explain low occurrence of critical events. However, it does not explain why low RR was associated with high occurrence of critical events; thus, further analysis is needed. On the other hand, higher than normal HR and RR were associated with higher occurrence of critical events, a result consistent with previous literature [22].

On the other hand, our study did not show a significant difference in occurrence of critical events in the ARS activation group and the non-activation group. This was contrary to the results of a systematic review of RRS in children, which found that RRS introduction lowered incidence by predicting critical events [23]. Furthermore, the results differed from the results of Tibballs et al.'s study [2], which is the basis of our ARS. We suspect that low compliance may have contributed to this conflicting result. For effective RRS, it is important that the patient is cared for in the PICU, but if the patient is in the early stage of deterioration, they will not be electively admitted to the PICU due to the lack of free beds. This may also be one of the explanations for the above result. Several previous literatures have suggested that the effectiveness of RRS may depend on the medical environment in which it is performed [8,24,25].

This study has several limitations. First it was conducted in a single center. Therefore, the medical specific environment of this hospital, such as the availability of beds in the PICU, likely affects the results and limits generalizability to other centers. However, this limitation is currently unavoidable because few

hospitals have introduced pediatric RRS, and moreover, it is the only center in Korea that has operated with a single parameter system for over 11 years. Second, there were almost no mental changes, perfusions, or urine output data among the ARS activators. We think it is more likely that this is due to low compliance, rather than that there were no cases with these characteristics. Seven parameters were needed to detect patient deterioration, which may have affected the outcome because our analysis relied on a half-system with only partial information. Lastly, in the process of calculating compliance, we used a simplified version consisting of four subdivided groups: SBP, HR, RR, and SpO_2. Therefore, there was room for underestimation in cases where ARS should have been activated. However, as mentioned earlier, there were few cases of actual activation due to mental changes, etc., thus the bias effect is not likely to be significant, which suggests the conclusion that compliance was bad.

In conclusion, this study showed that prediction of critical events by the ARS was excellent, but the sensitivity and PPV were poor. Additionally, the medical staff's compliance during the ARS activation process was also poor. There is a need for further studies of RRS that are more independent of subjective physician decision-making and consider a comprehensive set of factors.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.01354.

REFERENCES

1. Vincent JL, Einav S, Pearse R, Jaber S, Kranke P, Overdyk FJ, et al. Improving detection of patient deterioration in the general hospital ward environment. Eur J Anaesthesiol 2018;35:325-33.
2. Tibballs J, Kinney S, Duke T, Oakley E, Hennessy M. Reduction of paediatric in-patient cardiac arrest and death with a medical emergency team: preliminary results. Arch Dis Child 2005;90:1148-52.
3. Simchen E, Sprung CL, Galai N, Zitser-Gurevich Y, Bar-Lavi Y, Gurman G, et al. Survival of critically ill patients hospitalized in and out of intensive care units under paucity of intensive care unit beds. Crit Care Med 2004;32:1654-61.
4. Al-Moteri M, Plummer V, Cooper S, Symmons M. Clinical deterioration of ward patients in the presence of antecedents: a systematic review and narrative synthesis. Aust Crit Care 2019;32:411-20.
5. Parshuram CS, Dryden-Palmer K, Farrell C, Gottesman R, Gray M, Hutchison JS, et al. Effect of a pediatric early warning system on all-cause mortality in hospitalized pediatric patients: the EPOCH Randomized Clinical Trial. JAMA 2018;319:1002-12.
6. Choi YH, Lee HS, Lee BJ, Suh DI, Park JD. Effectiveness of bradycardia as a single parameter in the pediatric acute response system. Korean J Crit Care Med 2014;29:297-303.
7. Hall KK, Lim A, Gale B. The use of rapid response teams to reduce failure to rescue events: a systematic review. J Patient Saf 2020;16(3S Suppl 1):S3-7.
8. Trubey R, Huang C, Lugg-Widger FV, Hood K, Allen D, Edwards D, et al. Validity and effectiveness of paediatric early warning systems and track and trigger tools for identifying and reducing clinical deterioration in hospitalised children: a systematic review. BMJ Open 2019;9:e022105.
9. Edwards ED, Powell CV, Mason BW, Oliver A. Prospective cohort study to test the predictability of the Cardiff and Vale paedi-

atric early warning system. Arch Dis Child 2009;94:602-6.
10. Smith GB, Prytherch DR, Schmidt PE, Featherstone PI, Higgins B. A review, and performance evaluation, of single-parameter "track and trigger" systems. Resuscitation 2008;79:11-21.
11. Bell MB, Konrad D, Granath F, Ekbom A, Martling CR. Prevalence and sensitivity of MET-criteria in a Scandinavian University Hospital. Resuscitation 2006;70:66-73.
12. National Institute for Health and Care Excellence. Acutely ill adults in hospital: recognising and responding to deterioration [Internet]. National Institute for Health and Care Excellence; 2007 [cited 2023 Nov 1]. Available from: https://www.nice.org.uk/guidance/cg50
13. Subbe CP, Slater A, Menon D, Gemmell L. Validation of physiological scoring systems in the accident and emergency department. Emerg Med J 2006;23:841-5.
14. Hillman K, Chen J, Cretikos M, Bellomo R, Brown D, Doig G, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. Lancet 2005;365:2091-7.
15. Skaletzky SM, Raszynski A, Totapally BR. Validation of a modified pediatric early warning system score: a retrospective case-control study. Clin Pediatr (Phila) 2012;51:431-5.
16. Parshuram CS, Duncan HP, Joffe AR, Farrell CA, Lacroix JR, Middaugh KL, et al. Multicentre validation of the bedside paediatric early warning system score: a severity of illness score to detect evolving critical illness in hospitalised children. Crit Care 2011;15:R184.
17. Akre M, Finkelstein M, Erickson M, Liu M, Vanderbilt L, Billman G. Sensitivity of the pediatric early warning score to identify patient deterioration. Pediatrics 2010;125:e763-9.
18. Tucker KM, Brewer TL, Baker RB, Demeritt B, Vossmeyer MT. Prospective evaluation of a pediatric inpatient early warning scoring system. J Spec Pediatr Nurs 2009;14:79-85.
19. Duncan H, Hutchison J, Parshuram CS. The Pediatric Early Warning System score: a severity of illness score to predict urgent medical need in hospitalized children. J Crit Care 2006;21:271-8.
20. Kim L, Yun KS, Park JD, Lee B. Effect of diurnal variation of heart rate and respiratory rate on activation of rapid response system and clinical outcome in hospitalized children. Children (Basel) 2023;10:167.
21. Churpek MM, Yuen TC, Winslow C, Hall J, Edelson DP. Differences in vital signs between elderly and nonelderly patients prior to ward cardiac arrest. Crit Care Med 2015;43:816-22.
22. Rothschild JM, Gandara E, Woolf S, Williams DH, Bates DW. Single-parameter early warning criteria to predict life-threatening adverse events. J Patient Saf 2010;6:97-101.
23. Chong SL, Goh MS, Ong GY, Acworth J, Sultana R, Yao SH, et al. Do paediatric early warning systems reduce mortality and critical deterioration events among children?: a systematic review and meta-analysis. Resusc Plus 2022;11:100262.
24. Wee BY, Lee JH, Mok YH, Chong SL. A narrative review of heart rate and variability in sepsis. Ann Transl Med 2020;8:768.
25. Chapman SM, Wray J, Oulton K, Pagel C, Ray S, Peters MJ. 'The Score Matters': wide variations in predictive performance of 18 paediatric track and trigger systems. Arch Dis Child 2017;102:487-95.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):507-508
https://doi.org/10.4266/acc.2023.01480

| pISSN 2586-6052 | eISSN 2586-6060

Effect of combined reservoir mask oxygenation and high-flow nasal cannula in COVID-19 pneumonia

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The emergence of coronavirus disease 2019 (COVID-19) has created unprecedented challenges in respiratory care, necessitating the exploration of novel therapeutic interventions. Because the disease suddenly emerged and spread at a very rapid pace, numerous attempts were made to find the most appropriate respiratory support treatment [1]. Noninvasive respiratory support with reservoir mask oxygenation is usually considered the first-line choice for acute hypoxemic respiratory failure with COVID-19 pneumonia. A high-flow nasal cannula (HFNC) provides humidified and heated oxygen with increased tidal volume and end expiratory volume. In contrast, HFNC offers decreased dead space, respiratory rate, and work of breathing [2].

In this issue of Acute and Critical Care, Gur et al. [3] reported that dual oxygenation of reservoir mask and HFNC lowered 30-day mortality in patients with COVID-19 pneumonia. The value of this study is that addition of a reservoir mask to HFNC has been shown as one potential treatment option for COVID-19 pneumonia patients with hypoxemia. Although this study was retrospective and not randomized, it demonstrated its worth through success despite a propensity of variables such as gender, background diagnoses, laboratory findings, vital signs, and total administrated dose of glucocorticoids.

However, there was no significant difference in secondary outcomes and use of dual respiratory support modalities. Additionally, there are concerns that HFNC may increase the risk of cross-infection among healthcare providers and patients via aerosol and contamination of the HFNC circuit [4]. While the benefits of combined HFNC and reservoir mask oxygenation are compelling, high-level evidence supporting dual oxygenation remains limited [1]. Combined treatment of dual oxygenation presents a nuanced strategy in the management of COVID-19 pneumonia-related hypoxemic respiratory failure. Robust clinical trials are essential to establish its safety and efficacy in diverse patient populations.

Nevertheless, the combination of reservoir mask oxygenation and HFNC allows flexibility in adapting to the dynamic clinical course of COVID-19 pneumonia [5]. This enhanced oxygenation has the potential to alleviate hypoxemic respiratory failure more effectively than either therapy alone. The ability to adjust oxygen delivery based on individual patient needs may enhance treatment efficacy [6]. The potential advantages in terms of oxygenation and patient comfort, including resource implications, require further empirical validation [7]. During the pandemic, medical staff around the world experienced difficulties due to COVID-19, and an even more serious crisis may occur in the future. Consensus

Editorial

Received: November 10, 2023
Accepted: November 10, 2023

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guidelines for application of equivalence methodologies when treating COVID-19 with different phenotypes are under debate [8]. Continued research is essential to elucidate the true benefits and risks of this dual modality and to guide clinicians to optimize respiratory support for affected patients, even if only to guard against evolved forms of infection.

CONFLICT OF INTEREST

Dowan Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

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REFERENCES

1. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323:2329-30.
2. Whittle JS, Pavlov I, Sacchetti AD, Atwood C, Rosenberg MS. Respiratory support for adult patients with COVID-19. J Am Coll Emerg Physicians Open 2020;1:95-101.
3. Gur I, Zalts R, Dotan Y, Hussain K, Neuberger A, Fuchs E. Combining reservoir mask oxygenation with high-flow nasal cannula in the treatment of hypoxemic respiratory failure among patients with COVID-19 pneumonia: a retrospective cohort study. Acute Crit Care 2023;48:435-41.
4. Remy KE, Lin JC, Verhoef PA. High-flow nasal cannula may be no safer than non-invasive positive pressure ventilation for COVID-19 patients. Crit Care 2020;24:169.
5. Burnim MS, Wang K, Checkley W, Nolley EP, Xu Y, Garibaldi BT. The effectiveness of high-flow nasal cannula in coronavirus disease 2019 pneumonia: a retrospective cohort study. Crit Care Med 2022;50:e253-62.
6. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J 2020;56:2002130.
7. Nair PR, Haritha D, Behera S, Kayina CA, Maitra S, Anand RK, et al. Comparison of high-flow nasal cannula and noninvasive ventilation in acute hypoxemic respiratory failure due to severe COVID-19 pneumonia. Respir Care 2021;66:1824-30.
8. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):509-512
https://doi.org/10.4266/acc.2021.01452

| pISSN 2586-6052 | eISSN 2586-6060

Myoclonic status epilepticus after severe hyperthermia in a patient with coronavirus disease 2019

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Myoclonic status epilepticus (MSE) is a sign of severe neurologic injury in cardiac arrest patients. To our knowledge, MSE has not been described as a result of prolonged hyperpyrexia. A 56-year-old man with coronavirus disease 2019 presented with acute respiratory distress syndrome, septic/hypovolemic shock, and presumed community-acquired pneumonia. Five days after presentation, he developed a sustained fever of 42.1°C that did not respond to acetaminophen or ice water gastric lavage. After several hours, he was placed on surface cooling. Three hours after fever resolution, new multifocal myoclonus was noted in the patient's arms and trunk. Electroencephalography showed midline spikes consistent with MSE, which resolved with 40 mg/kg of levetiracetam. This case demonstrates that severe hyperthermia can cause cortical injury significant enough to trigger MSE and should be treated emergently using the most aggressive measures available. Providers should have a low threshold for electroencephalography in intubated patients with a recent history of hyperpyrexia.

Key Words: brain injury; coronavirus disease 2019; fever; hyperthermia; myoclonus; status epilepticus

Case Report

Received: October 6, 2021
Revised: November 20, 2021
Accepted: November 22, 2021

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Myoclonic status epilepticus (MSE) is most frequently associated with cardiac arrest and is often considered a sign of severe neurologic injury [1-3]. To our knowledge, MSE has not previously been described as a result of hyperpyrexia. Here we present the case of a man with coronavirus disease 2019 (COVID-19) who developed MSE following prolonged hyperpyrexia.

CASE REPORT

A 56-year-old man with a history of hypertension and poorly controlled diabetes mellitus complicated by chronic osteomyelitis presented to the hospital with 1 week of lethargy and poor appetite and 2 days of diarrhea. He was febrile at 38.3°C, had a heart rate of 150 to 180 bpm, and SpO_2 of 87% on a non-rebreather. Nasopharyngeal polymerase chain reaction testing returned a positive result for COVID-19. One hour after hospital arrival, he became acutely dyspneic and hypoxic. He was intubated for hypoxemic respiratory failure and

treated for acute respiratory distress syndrome, mixed septic/hypovolemic shock, and presumed community-acquired pneumonia. He was administered dexamethasone, remdesivir, ceftriaxone, vancomycin, and doxycycline.

Five days after his initial presentation, the patient became febrile at a maximum temperature of 42.1°C with new leukocytosis of 24,700/μL, up from 7,600/μL. He was given acetaminophen and ice water gastric lavage and transferred to surface cooling after several hours given a lack of response to the aforementioned measures. He sustained a fever above 41°C for 6 total hours. His creatine kinase concentration was 1,763 units/L, up from 301 units/L, and results of urinalysis and blood culture were unremarkable. Treatment was broadened to include vancomycin, ceftriaxone, and ampicillin for empiric central nervous system (CNS) coverage. Lumbar puncture performed during his fever showed an opening pressure of 25 mm Hg, three erythrocytes, two nucleated cells, a protein concentration of 40.7 mg/dL, and a glucose level of 143 mg/dl (serum glucose level, 211 mg/dl). Chest X-ray showed diffuse pulmonary opacities, unchanged from prior imaging. The lowest recorded blood oxygen level (SpO_2) was 92%. His sputum culture ultimately grew *Stenotrophomonas*, and he was placed on a trimethoprim and sulfamethoxazole combination regimen.

Three hours after his fever resolved, the patient showed new multifocal myoclonus in his arms and trunk. He was unresponsive to painful stimuli. Arterial blood gas was notable at pH 7.4, partial pressure of carbon dioxide of 39 mm Hg, and partial pressure of oxygen of 130 mm Hg. Electroencephalography showed midline spikes consistent with MSE (Figure 1), which resolved with 40 mg/kg of levetiracetam. He was maintained on 750 mg of levetiracetam twice daily and was treated with acetaminophen for fever suppression and surface cooling with a target temperature of 36°C due to a concern for cortical injury related to his hyperpyrexia. Surface cooling was discontinued after 72 hours. Neuron-specific enolase peaked at 81.3 ng/ml the day after the fever and returned to within the normal range 2 days later.

Magnetic resonance imaging of the brain was not performed until 12 days post-fever due to patient instability and did not demonstrate any signs of cortical or metabolic injury (Figure 2). Forty days after his episode of MSE, the patient began following simple commands with his eyes, but he experienced no further neurologic recovery. His course was complicated by multiorgan failure and multiple brain infarcts, and he passed away 75 days after hospital admission.

DISCUSSION

MSE has been reported in diverse settings, including metabolic encephalopathy, degenerative CNS disorders, generalized epilepsy, and drug reactions [3,4]. However, it is most frequently associated with cardiac arrest [1-3]. MSE in cardiac arrest patients is considered a poor prognostic indicator and is associated with a high fatality rate [1-3]. Despite its grim prognosis, there are several case reports of recovery following

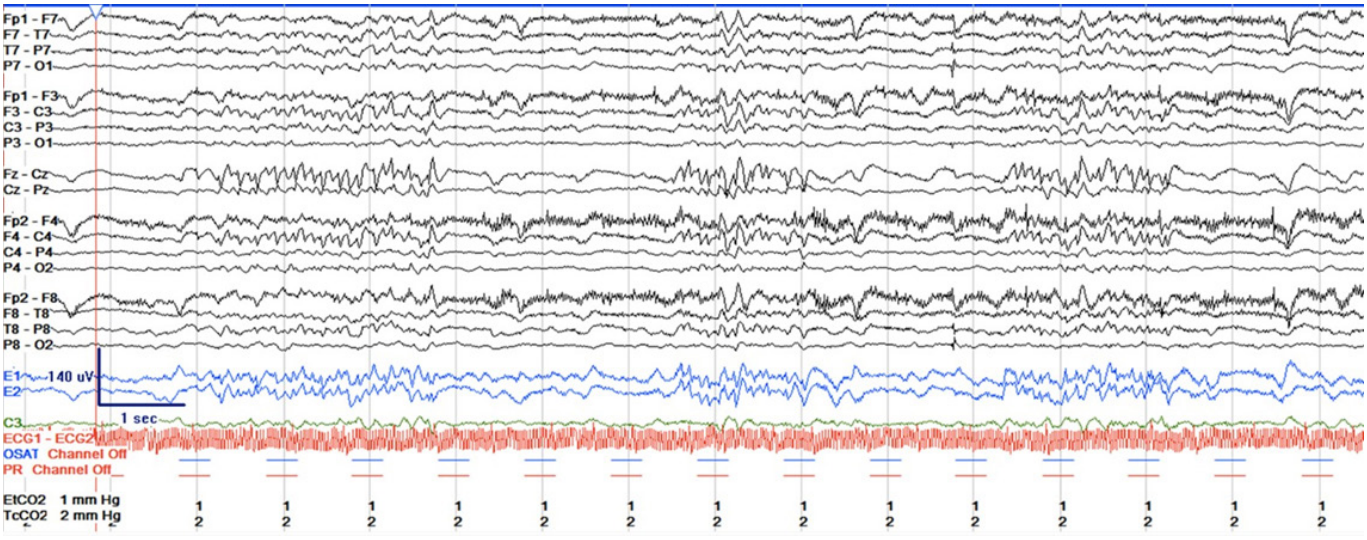

Figure 1. Electroencephalogram taken after fever resolution shows midline spikes.

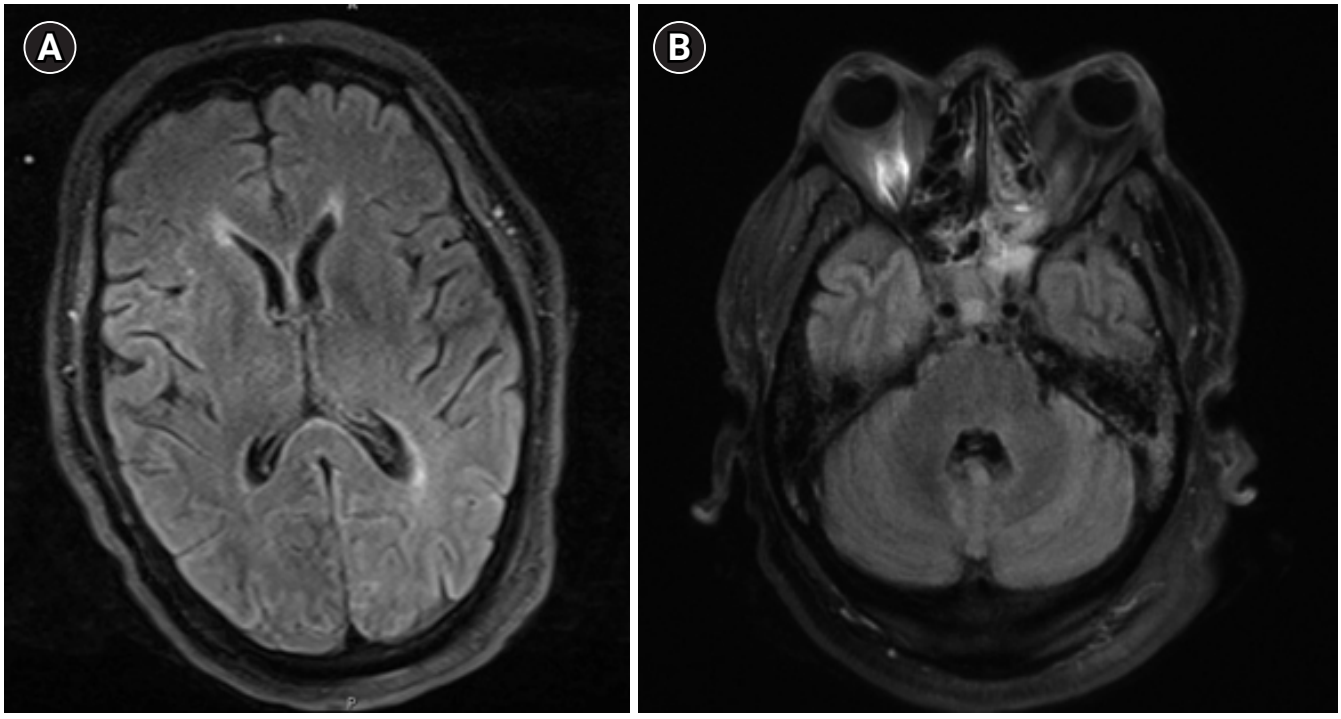

Figure 2. (A, B) Brain magnetic resonance imaging taken 12 days after fever resolution did not demonstrate cortical or metabolic injury.

MSE [3,5]. Unfortunately, our patient experienced minimal neurologic recovery and passed away following a prolonged hospital stay. MSE is frequently refractory to anti-epileptic therapy, which diverges from the experience in our patient, who responded well to levetiracetam [1-3].

Given his new leukocytosis at the time of fever and the sputum culture positive for *Stenotrophomonas*, our patient's hyperpyrexia was likely secondary to pneumonia. Previous case reports have described MSE secondary to COVID-19 pneumonia and anoxia [3,5]. Although it is possible that the MSE in this patient was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or pneumonia, our patient's normal SpO_2 and arterial blood gas values together with lack of other metabolic derangements and the tight temporal correlation between fever and MSE onset all suggest that hyperpyrexia was the primary cause.

To our knowledge, MSE has not previously been described as a result of prolonged hyperpyrexia. Nonetheless, there is increasing recognition that hyperthermia of any etiology can cause neurologic injury [6,7]. Hyperthermia-induced injury is most common in the cerebellum but can affect many components of the CNS, including the basal ganglia, brainstem, and cerebral cortex [6]. The mechanism of neurologic injury is likely multifactorial. Hyperthermia has been shown to directly affect neurons through variable mechanisms, including denaturation, apoptosis, mitochondrial damage, and excitotoxicity from elevated levels of excitatory neurotransmitters in vitro and in animal models [6,7]. Other potential mechanisms demonstrated in animal and human models include disruption of the blood–brain barrier, changes in cerebral blood flow, and inflammatory cytokine response [6,8,9].

The pro-inflammatory cytokine response might be of particular importance in patients with COVID-19. Both infection by SARS-CoV-2 and hyperthermia cause a pro-inflammatory cascade that leads to the release of inflammatory cytokines, including tumor necrosis factor, interleukin (IL)-1, and IL-6 [6,8-10]. An elevated IL-6 concentration in particular is associated with a greater severity of symptoms in patients with heat stroke or COVID-19 [6,8-10]. Our patient likely suffered a double burden of cytokine release from his underlying SARS-CoV-2 infection and his high fever.

This case demonstrates that severe hyperthermia can cause cortical injury significant enough to trigger MSE. Hyperthermia to the extent seen in our patient should be treated emergently with the most aggressive measures available due to the possibility of devastating neurological injury. Our patient ultimately responded to surface cooling, which was initiated only after failure of more conservative procedures. Finally,

providers should have a low threshold for electroencephalography in intubated patients with a recent history of severe hyperthermia.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

Consent to publish the case report was obtained from the patient's next of kin.

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AUTHOR CONTRIBUTIONS

Conceptualization: SMS. Investigation: all authors. Data Curation: KAH, JJP. Writing–original draft: KAH. Writing–review & editing: all authors.

REFERENCES

1. Wijdicks EF, Parisi JE, Sharbrough FW. Prognostic value of myoclonus status in comatose survivors of cardiac arrest. Ann Neurol 1994;35:239-43.
2. Hui AC, Cheng C, Lam A, Mok V, Joynt GM. Prognosis following postanoxic myoclonus status epilepticus. Eur Neurol 2005;54:10-3.
3. Celesia GG, Grigg MM, Ross E. Generalized status myoclonicus in acute anoxic and toxic-metabolic encephalopathies. Arch Neurol 1988;45:781-4.
4. Baysal Kirac L, Aydogdu I, Acarer A, Alpaydin S, Bayam FE, Onbasi H, et al. Myoclonic status epilepticus in six patients without epilepsy. Epilepsy Behav Case Rep 2012;1:10-3.
5. Chen W, Toprani S, Werbaneth K, Falco-Walter J. Status epilepticus and other EEG findings in patients with COVID-19: a case series. Seizure 2020;81:198-200.
6. Walter EJ, Carraretto M. The neurological and cognitive consequences of hyperthermia. Crit Care 2016;20:199.
7. White MG, Luca LE, Nonner D, Saleh O, Hu B, Barrett EF, et al. Cellular mechanisms of neuronal damage from hyperthermia. Prog Brain Res 2007;162:347-71.
8. Hashim IA, Al-Zeer A, Al-Shohaib S, Al-Ahwal M, Shenkin A. Cytokine changes in patients with heatstroke during pilgrimage to Makkah. Mediators Inflamm 1997;6:135-9.
9. Hammami MM, Bouchama A, Al-Sedairy S, Shail E, AlOhaly Y, Mohamed GE. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. Crit Care Med 1997;25:1314-9.
10. Narula N, Joseph R, Katyal N, Daouk A, Acharya S, Avula A, et al. Seizure and COVID-19: association and review of potential mechanism. Neurol Psychiatry Brain Res 2020;38:49-53.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):513-514
https://doi.org/10.4266/acc.2023.01228

| pISSN 2586-6052 | eISSN 2586-6060

Right-sided infective endocarditis of a native valve with multiple embolus lesions

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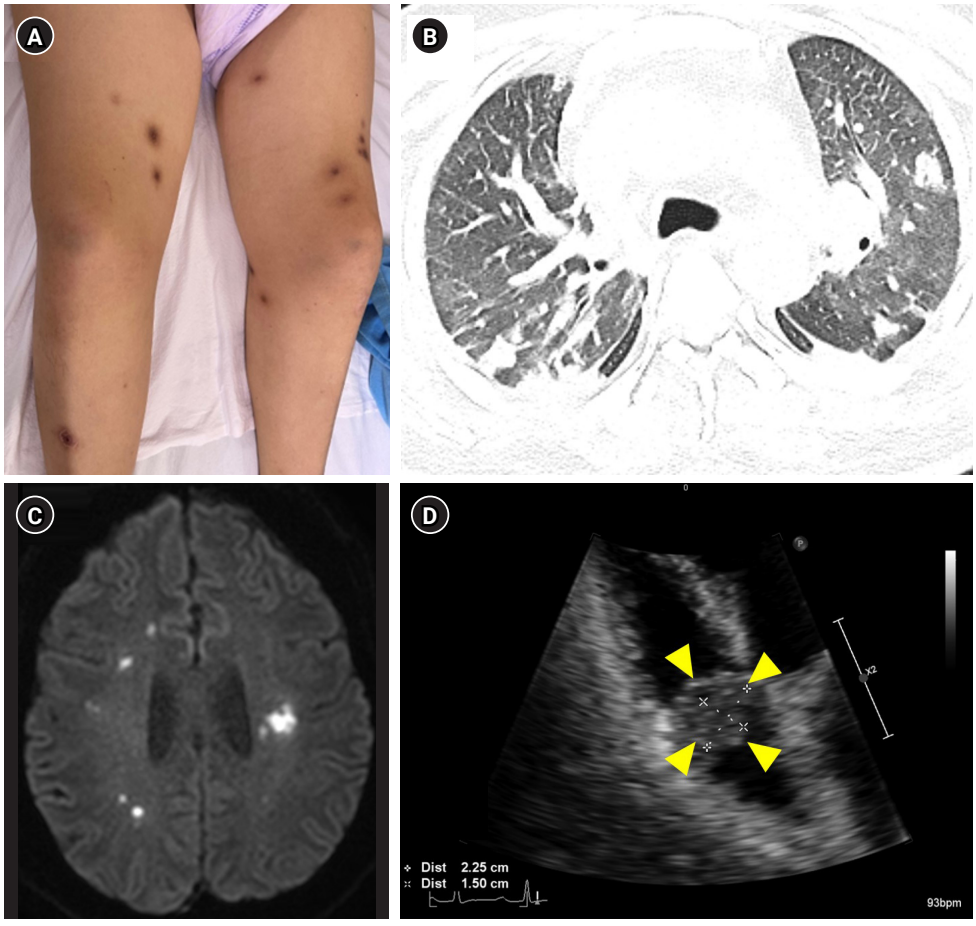

Figure 1. (A) Multiple dot-like black erythematous lesions measuring 1–3 cm throughout the body. (B) Chest computed tomography revealing multiple nodules in both lungs. (C) Diffusion-weighted brain magnetic resonance imaging of lesions with high signal intensity, appearing as multiple scattered dots, in both fronto-parieto-temporal lobes. (D) Apical view of the four chambers on transthoracic echocardiography showing vegetation in the tricuspid valve indicated by yellow arrowheads.

Image in Critical Care

Received: September 22, 2023
Revised: October 24, 2023
Accepted: October 26, 2023

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A 47-year-old man was transferred to our hospital with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. On admission, the patient had multiple 1–3-cm-sized black dotlike erythematous lesions throughout the body (Figure 1A). In addition, he had multiple patchy consolidations in both lung fields (Figure 1B) and multifocal dots scattered in both fronto-parieto-temporal lobes (Figure 1C). On the 2nd day of admission, transthoracic echocardiography revealed a 2.25×1.5-cm-sized friable mass in the tricuspid septal leaflet (Figure 1D, Supplementary Videos 1 and 2). MRSA was isolated from the patient's blood and skin lesions. Unexpectedly, no intracardiac shunt was shown on transthoracic and transesophageal echocardiography. Tricuspid septal leaflet repair and mass debridement had been performed in the referring hospital. MRSA was isolated from the debrided mass from the tricuspid valve.

In this case, atypical features were noted. Infective endocarditis occurred on a normal tricuspid valve, and a large vegetation was present, caused by MRSA. He also exhibited clinical signs of systemic embolization, despite the absence of congenital heart disease, central venous catheter use, and drug use, making this case particularly unique and challenging to diagnose and treat [1,2].

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

This study was approved by the Institutional Review Board at Jeju National University Hospital (No. 2023-07-006). The patient provided informed consent for publication of the report.

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Conceptualization: JRY. Data curation: JRY, KYB. Formal analysis: JRY. Methodology: JRY, MK. Project administration: JRY. Visualization: JRY. Writing–original draft: MK. Writing–review & editing: JRY.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2023.01228.

REFERENCES

1. Shmueli H, Thomas F, Flint N, Setia G, Janjic A, Siegel RJ. Right-sided infective endocarditis 2020: challenges and updates in diagnosis and treatment. J Am Heart Assoc 2020;9:e017293.
2. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al, ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):515
https://doi.org/10.4266/acc.2017.00528.e1

| pISSN 2586-6052 | eISSN 2586-6060

A successful application of adult polymyxin B–immobilized fiber column hemoperfusion to a neonate with septic shock

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Acute and Critical Care 2019;34:284-8
https://doi.org/10.4266/acc.2017.00528

Corrigendum

Received: October 19, 2023
Accepted: October 19, 2023

In the article entitled "A successful application of adult polymyxin B-immobilized fiber column hemoperfusion to a neonate with septic shock", there was an error in the affiliation of one of the authors (Hyungtae Kim). The correct affiliation for the author should be:

Department of Thoracic and Cardiovascular Surgery, Pusan National University Yangsan Hospital, School of Medicine, Pusan National University

Acute and Critical Care

Acute and Critical Care 2023 November 38(4):516
https://doi.org/10.4266/acc.2022.01424.e1

| pISSN 2586-6052 | eISSN 2586-6060

Comparison of safety and efficacy between therapeutic or intermediate versus prophylactic anticoagulation for thrombosis in COVID-19 patients: a systematic review and meta-analysis

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Acute and Critical Care 2023;38:160-71
https://doi.org/10.4266/acc.2022.01424

Corrigendum

Received: November 20, 2023
Accepted: November 20, 2023

In the article entitled "Comparison of safety and efficacy between therapeutic or intermediate versus prophylactic anticoagulation for thrombosis in COVID-19 patients: a systematic review and meta-analysis," there was an error in Results section of the abstract. In the sentence "In the severe patients, the incidence of thromboembolic and bleeding events in the therapeutic or intermediate." should be:

"In the severe group, the incidence of thromboembolic and bleeding events in the therapeutic and prophylaxis groups was not statistically different."

Furthermore, the city of Myongji Hospital was inadvertently omitted, and it should be included as "Goyang."

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Acute and Critical Care

| pISSN 2586-6052 | eISSN 2586-6060

Instructions for Authors

1992. 5. 13. Enacted
2017. 2. 22. Revised
2017. 5. 17. Revised
2018. 5. 21. Revised
2018. 11. 23. Revised
2021. 12. 1. Revised

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Conceptualization: MHC. Data curation: JH. Formal analysis: YIA. Funding acquisition: MHC. Methodology: MHC, JH, YIA. Project administration: YIA. Visualization: MHC, JH, YIA. Writing – original draft: JH, YIA. Writing – review & editing: MHC, JH, YIA.

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2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
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B. Book

Authors. Book title. Edition*. Publisher; Published year.

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4. Nuwer MR. Evoked potential monitoring in the operating room. 2nd ed. Raven Press; 1986.

C. Book Chapter

Authors of chapter. Title of chapter. In: Editors of book, editor(s). Title of book. Edition. Publisher; Published year. p. Start-End page.

5. Blitt C. Monitoring the anesthetized patient. In: Barash PG, Cullen BF, Stoelting RK, editors. Clinical anesthesia. 3rd ed. Lippincott-Raven; 1997. p. 563-85.

D. Electronic Format

• Electronic publication before print

6. Lee OJ, Cho YH, Hwang J, Yoon I, Kim YH, Cho J. Long-term extracorporeal membrane oxygenation after severe blunt traumatic lung injury in a child. Acute Crit Care 2017 Feb 10 [Epub]. https://doi.org/10.4266/acc.2016.00472

• Website

7. Sage Terapeutics. A study with SAGE-547 for superrefractory status epilepticus [Internet]. U.S. National Library of Medicine; 2000 [cited 2016 Nov 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT02477618?term=NCT02477618&rank=1

14) Tables

Each table should be consecutively typed or printed on a separate sheet of paper in the order of citation in the text. Supply a brief title at the top of the table. The titles of tables start with "Table 1." Footnotes should be provided consecutively in order of the information, statistics, and abbreviations. Footnoted information should be referenced using small letters (ex; a), b)) in alphabetical order.

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