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Original article

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Conservative management of Covid 19 associated hypoxemia

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Take home message:

Permissive hypoxemia where the decision to intubate is based on the clinical picture and oxygen content is feasible in the acute phase of Covid 19

Abstract:

Background:

Invasive mechanical ventilation of hypoxemic Covid 19 patients is associated with mortality rates of more than 50 %. We evaluated clinical outcome data of two hospitals that agreed on a predefined protocol for restrictive use of invasive ventilation where the decision to intubate was based on the clinical presentation and oxygen content rather than on the degree of hypoxemia.

Method:

Data analysis of patients with positive PCR-testing for SARS-CoV-2, typical history, and symptoms and pulmonary infiltrates who exhibited oxygen saturation values of less than 93 %.

Results:

We identified 78 patients who met the inclusion criteria. The SaO2 nadir was 84.4 ± 6.5 % for the whole group. Fifty-three patients (68%) received nasal oxygen (group1), 17 patients (22%) were treated with nasal high-flow, CPAP, non-invasive ventilation, or a combination thereof (group 2) and 8 patients (10%) were intubated (group 3). The Horovitz index was 216 ± 8 for group 1, 157 ± 13 for group 2, and 106 ± 15 for group 3. Oxygen content was 14.5 ± 2.5, 13.4 ± 1.9, and 11.6 ± 2.6 ml/dl for the three respective groups. Overall mortality was 7.7 %, the mortality of intubated patients was 50 %. 93 % of patients could be discharged on room air.

Conclusion:

Permissive hypoxemia where decisions for the level of respiratory therapy were based on the clinical presentation and oxygen content resulted in low intubation rates, low overall mortality, and a low number of patients who require oxygen after discharge.

Introduction:

Although COVID-19 is asymptomatic to mild in about 80% of cases, about 15% of patients show a severe and about 5% a critical course, which is usually based on lung involvement with respiratory failure[1]. The first therapeutic recommendations therefore addressed hypoxemia in particular with the aim of keeping oxygen saturation above at least 90%[2]. Some authors even advise caution against the use of high-flow oxygen administration (NHF) and non-invasive ventilation (NIV) in acute hypoxemic respiratory insufficiency in the context of COVID-19 and call for early intubation[3], and some researchers even recommend intubation and invasive ventilation already if the Horovitz index [4] is 200 or lower [5]. In general, hypoxemia is an accepted indication for intubation in Covid 19 patients[6][7][8]. The work of Raaof et al. provides a good overview about the respiratory support recommendations of the different countries and societies in the context of Covid 19 disease[9] . The prognosis of invasively ventilated Covid 19 patients however is poor and mortality ranges somewhere around 50 % and higher, especially in older patients[10][11][12]. The fact that there is a large discrepancy between oxygen saturation and the extent of dyspnoea has given rise to the term 'happy hypoxemia'[13] in Covid 19 patients. The pathophysiological mechanisms of this phenomenon are being discussed currently [13][14][15][16][17] as well as the impact of happy hypoxemia on respiratory management[14][18]. A recent Cochrane review did not find evidence, that higher oxygen targets benefit patients with respiratory failure[19]. Hypoxemia can either be caused by intrapulmonary shunting or ventilation-perfusion mismatch which in Covid 19 is mainly caused by diffusion impairment. Only the latter is responsive to supplemental oxygen[20]. Dyspnoea on the other hand poorly correlates to hypoxemia[21]. In the presence of inflammatory diseases (such as Sars-Cov-2 infections), hypoxemia is frequently being caused by other mechanisms such as stimulation of irritant, stretch, and J receptors[22] or activation of respiratory muscles[23]. Focusing on tissue hypoxia oxygen delivery (DO2), determined by oxygen content (CaO2) and cardiac output (CO) is crucial. Critical values for CaO2 with signs of anaerobic metabolism occur in animal models at levels below 9 mlO2/dl blood, which corresponds to an oxygen saturation of approximately 50% at normal haemoglobin levels and normal cardiac output[24]. Experiments in healthy humans have shown, that the critical level for oxygen content is lower than 6.6 (ml/dl)[25]. In particular lung tissue is vulnerable to oxygen concentrations of more than 21% and it is well known that oxygen per se is toxic if given in high concentrations an can cause ARDS in animal

models [26].This leads to the question, if a higher tolerance of hypoxemia and a preferred use of non-invasive respiratory support instead of intubation and decision making based on the clinical presentation as previously suggested should be preferred [18] and can improve outcome in Covid 19 patients. Based on these considerations we analysed the data of all hypoxemic Covid 19 patients in two hospitals that had previously agreed on such a protocol for the treatment of respiratory failure in COVID-pneumonia.

Method:

Treatment protocol:

At the beginning of the pandemic, we have developed a predefined protocol for COVID-19 therapy in our hospitals. For the treatment of respiratory insufficiency, we have defined a strategy that provides invasive ventilation only when other measures have failed to stabilize the patient and intubation appears to be vital. The primary goal is to maintain the patient's spontaneous breathing for as long as possible. Positioning techniques such as prone or lateral position are to be used at each therapy stage - even under room air, oxygen therapy or non-invasive ventilation. Furthermore, we follow the principle of Hippocrates "primum non nocere" and have excluded the use of experimental procedures such as the use of hydroxchloroquine, Lopinavir/Ritonavir, Tocilizumab or Remdesivir. Patients received a pneumococcal active antibiotic (ampicillin /sulbactam) in combination with a macrolide as well as prophylactic doses of heparin. Whenever possible patients were mobilized as early as possible.

The two participating pulmonary facilities (Kloster Grafschaft, facility 1 and Bethanien Moers, facility 2) agreed on the following protocol:

Respiratory support should be given in the following escalating sequence (figure 1).

Escalation to the next level was made if the patients clinical work of breathing required the next level of support or the oxygen content was determined to be below 9 ml/dl. Hypoxemia per se was not an indication to escalate (permissive hypoxemia).

Inclusion criteria:

Patients had to be primarily admitted to one of the investigational sites. Patients who were transferred from other hospitals with prior treatment (e.g. who were already intubated) were excluded.

Patients had to be Sars-CoV-2 PCR positive and had to have infiltrates on conventional chest X-ray or CT scan. Only patients with an oxygen saturation (SaO2) of less than 93 % were included into the analysis. All patients were treated in an intermediate care or intensive care setting with continuous monitoring of oxygen saturation and heart rate by pulse oximetry. Patients were seen at least daily by a senior physician and laboratory tests were done at least every other day. Respiratory therapists were readily available to deliver respiratory support.

Data were retrospectively collected by chart review and transferred into a concerted Excel database at the respective site.

The responsible ethics commission approved the retrospective analysis (AEKWL 2020-897-f-S)

Statistics:

Continuous variables are presented as means (± SD), and categorical variables as numbers and frequency (percentages). All data was transferred to SPSS (version 27, IBM, Armonk, NY, USA) for further analysis. Multiple comparison of continuous variables was performed by means of ANOVA. For post-hoc analysis we used a t-test with Bonferroni adjustment for multiple comparisons. A p of < 0,05 was used as the significance threshold. Missing data was handled by pairwise deletion.

Results:

We identified a total of 78 patients who met the inclusion criteria (26 from facility 1 and 52 from facility 2). Mean hospital length of stay was 14.5 ± 13.5 days. Basic demographic data and pre-existing comorbidities are shown in table 1:

Number of patients	78
Male (%)	56.4
Caucasian (%)	100
Age (years ± SD)	65 ± 14
BMI (kg/m^2 ± SD)	29.4 ± 4.9
Active smoker	16.7 %
Former Smoker	46.2 %
Non smoker	37.2 %
Hypertension	70.5 %
Diabetes	19.2 %
Coronary artery disease	21.8 %
Asthma	17.9 %
COPD	10.3 %
Malignancy	21.8 %

Table 1: Basic demographic data and pre-existing comorbidities (SD = standard deviation)

On admission 87.2 % of the patients experienced dyspnoea. Anosmia was present in 30.8 % of patients and 84.6 % reported fatigue. Bilateral infiltrates on chest x-ray or CT scan were present in 97.5 % of patients, only 2.5 % had unilateral infiltrates. Overall admission SaO2 was 92 ± 5.8 %, the lowest reported oxygen saturation during the hospital course was 84.4 ± 6.5 %.

For further analysis we grouped patients according to the maximal respiratory treatment as shown in figure 1. This group distribution is shown in figure 2. The lowest reported oxygen saturation within these groups is shown in figure 3. The lowest reported Horovitz index is shown in Figure 4. The lowest measured oxygen content is shown in figure 5.

Laboratory values according to maximal treatment is shown in table 2:

	only oxygen (1) N=53	NHF/CPAP/NIV (2) N=17	invasive MV (3) N=8
Age	65 ± 15	62 ± 13	73 ± 9
BMI	29.4 ± 5.2	29.6 ± 5.1	29.1 ± 2.5
LOS (days)	10.1 ± 6.7$^{(2,3)}$	19.3 ± 11.8$^{(1,3)}$	34 ± 26.9$^{(1,2)}$
temperature °C	38.3 ± 1$^{(2)}$	39.1 ± 0.9 $^{(1)}$	39.1 ± 0.5
SaO2 (%)	93.1 ± 3.7$^{(3)}$	91.6 ± 6$^{(3)}$	85.4 ± 10.6 $^{(1,2)}$
respiratory rate /min	20.6 ± 4.4$^{(2)}$	25.7 ± 6.7 $^{(1)}$	23.5 ± 7.6
heart rate /min	90 ± 20	99 ± 16	95 ± 21
RR systolic (mmHg)	118 ± 21	110 ± 22	103 ± 23
RR diastolic (mmHg)	69 ± 11	68 ± 10	63 ± 13
Hemoglobin nadir (mg/dl)	12.4 ± 1.9	12.1 ± 2	11 ± 2.4
Leucocytes nadir /µl	5745 ± 2732	5724 ± 2602	5512 ± 1629
Lymphocytes nadir/µl	986 ± 2015	553 ± 262	469 ± 342
LDH max (U/l)	405 ± 129$^{(2,3)}$	562 ± 260$^{(1,3)}$	741 ± 190$^{(1,2)}$
BNP max (pg/ml)	1773 ± 3086	669 ± 895$^{(3)}$	5258 ± 7659$^{(2)}$
CRP max (mg/dl)	10.9 ± 7.1$^{(2,3)}$	21.6 ± 9.2$^{(1)}$	26.4 ± 12.3$^{(1)}$
PCT max (ng/ml)	0.9 ± 2$^{(3)}$	0.8 ± 1.2$^{(3)}$	3 ± 2.9$^{(1,2)}$
Creatinine max (mg/dl)	1.25 ± 0.62$^{(3)}$	1 ± 0.3$^{(3)}$	2.6 ± 1.4$^{(1,2)}$
D-Dimer max (ng/ml)	1530 ± 1575$^{(3)}$	2698 ± 2464	6574 ± 5321$^{(1)}$
Troponin max (µg/l)	28.5 ± 39$^{(3)}$	25.9 ± 33.1$^{(3)}$	467 ± 1047$^{(1,2)}$
PO_2 nadir (mmHg)	54.5 ± 11	47.8 ± 10.5	45.9 ± 6.8

Table 2: Demographic, physiological and laboratory data according to treatment groups. LOS = length of (hospital) stay, SaO2 = oxygen saturation, RR = blood pressure, LDH = lactate dehydrogenase, BNP = brain natriuretic peptide, CRP = C-reactive protein, PCT = procalcitonin, PO_2 = partial pressure of oxygen, nadir = lowest measured value, max =

maximal measured value. Number in brackets indicate significant differences to the respective column ($p < 0.05$)

All patients received beta-lactam antibiotics, 97.4 % of patients received an additional macrolide. Systemic anticoagulation was given in 88.5 % of patients. Since our data were collected before data from the Recovery trial were published[27], dexamethasone was not given as the standard of care. Outcome, respectively respiratory treatment on discharge, is shown in figure 6. The overall mortality was 7.7 %, the mortality rate of intubated patients was 50 %. The two patients who died on oxygen treatment were 86 and 96 years of age and had declared to refuse any form of respiratory support beyond oxygen administration in their living will. Reasons for intubation in eight patients were septic shock on admission in one patient, cardiac arrest due to AV-block 3 in one patient and NIV failure according to our protocol in six patients.

Discussion:

Our escalation protocol of respiratory support measures that was based on the clinical presentation and oxygen content rather than on markers of oxygenation or the Horovitz index resulted in an intubation rate of only 10.3 % and an overall mortality of 7.7 %. Our mortality rate of 50 % in intubated patients is comparable to previous published data[10][11][12]. The overall mortality of patients hospitalized for Sars-CoV-2 infections in Germany is 22% [11] and is thus much higher than in our study in which only hypoxemic patients were included. Raaof et al. has already pointed out the various therapeutic approaches of different countries and societies with regard to the treatment of respiratory insufficiency. Randomized trials on this issue are unlikely to be conducted during the current pandemic. Thus, comparisons of different treatment strategies of different cohorts within the same health care system can be helpful to judge on treatment efficiency. Roedl and co-workers reported retrospective data on a large cohort in the city of Hamburg(26). They reported, that 167 (75 %) of ICU patients received invasive mechanical ventilation within a median of one day after admission while NHF or NIV was only used in 18 % of patients prior to intubation with high failure rates. In addition, PO2 levels were higher (70 mmHg in survivors and 64 mmHg in non-survivors of mechanical ventilation) compared to our cohort (see table 2) indicating, that the decision to intubate was probably done more progressively. ICU survival rates were 44 % in ventilated and 35 % in not ventilated patients and thus were

much higher than the rate we reported (7.7%). Burns and co-workers found an improved survival when NIV was given to frail patients who were not deemed appropriate for invasive mechanical ventilation and proposed a general integrated escalation strategy of non-invasive respiratory therapies to avoid intubation[29]. Patel et al. worked with a respiratory escalation scheme in moderate to severe hypoxemic Covid 19 patients, that was comparable to ours[30]. Their decision to intubate was also based on clinical presentation but the oxygen saturation goal was 94 % and the ratio of intubated patients was 36 %. Our protocol did not call for an oxygen saturation goal, which might explain the lower intubation rate of 10.3 %. Brusasco and co-workers reported a CPAP success rate of 83 % in Covid 19 patients with a mean PaO_2 / FiO_2 ratio of 119. Oranger et al. decreased the combined outcome of intubation and/or death significantly from 57 % down to 23 % after a protocol of routine CPAP use was introduced to hypoxemic Covid 19 patients[31]. The patient's well tolerance of hypoxemia has led to the term 'happy hypoxemia'[13]. Hypoxemia hardly causes dyspnoea [21], and dyspnoea is more related to hypercapnia, acidosis [32] or activation of the respiratory muscles[23]. Hypoxemia as measured by arterial blood gas analysis or pulse oximetry does not equal tissue hypoxia.

Oxygen delivery to the cells is being determined by the oxygen content

(**1.34 x haemoglobin (mg/dl) x oxygen saturation (%) / 100** + 0.0031 x partial pressure of oxygen (mmHg))

times the cardiac output. The majority of oxygen (98%) is bound to haemoglobin (bold printed part of the equation) while the amount of freely dissolved oxygen (underlined part of the equation) is negligible. Lowering the saturation by X % has the same effect as lowering the haemoglobin by X %. So why we are more concerned about severe hypoxemia than about severe anaemia? The latter was not present in our patients as shown in table 2 which might in part explain the good tolerance of hypoxemia.

Elevated body temperature (fever) as seen in our patients shifts the oxygen dissociation curve to the right which facilitates the release of oxygen in the periphery[33]. A lack of oxygen on the cellular level does not occur until the oxygen delivery has decreased to 25% of the normal value[34]. In animal models anaerobic metabolism occurred if the oxygen content fell below 9 ml/dl[24]. Lieberman and co-workers had shown, that lowering the oxygen content to as low as 6.6 ml/dl did not cause signs of anaerobic metabolism in healthy volunteers[25]. Our threshold of 9 ml/dl appeared to be safe in our patient cohort.

Based on these considerations, the clinical importance of hypoxemia should not be overestimated especially since invasive ventilation might correct hypoxemia short term but

may inflict ventilator associated lung injury[35] or oxygen induced ARDS[26]. A more restrictive use of invasive mechanical ventilation and oxygen as suggested recently [18], might be advised. Our data suggest that such a strategy is more beneficial for Covid 19 patients.

We observed the typical laboratory abnormalities as seen in previous investigations[30][36]. Previous investigations have shown, that there is great potential to recover from Covid 19 with very little sequelae[37]. It should be particularly emphasized that the majority (93%) of the patients who survived could be discharged without oxygen. Only four patients treated with NHF/CPCP/NIV required oxygen on discharge and one patient who was intubated required tracheostomy and continued on invasive ventilation. Our data suggest that the lungs recover well from Covid 19 if they are denied the stress of invasive ventilation and over-oxygenation.

Conclusion:

A respiratory support escalation scheme based on clinical appearance and oxygen content rather than on the level of oxygenation (permissive hypoxemia) is feasible and has a favourable outcome in our retrospective analysis. Hypoxemia per se should not be an indication for invasive mechanical ventilation. The vast majority of patients recover well from Covid 19 if such a strategy is pursued.

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Figure legends:

Figure 1: Escalation sequence (CPAP = continuous positive airway pressure)

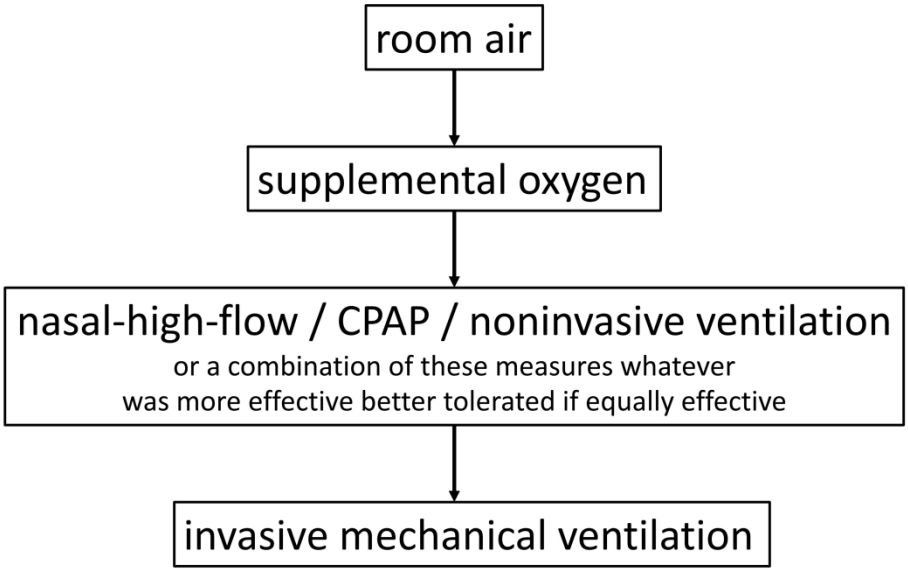
Figure 2: Distribution of the highest level of respiratory support that was delivered to the patient (NHF = nasal high-flow, CPAP = continuous positive airway pressure, NIV = non-invasive ventilation).

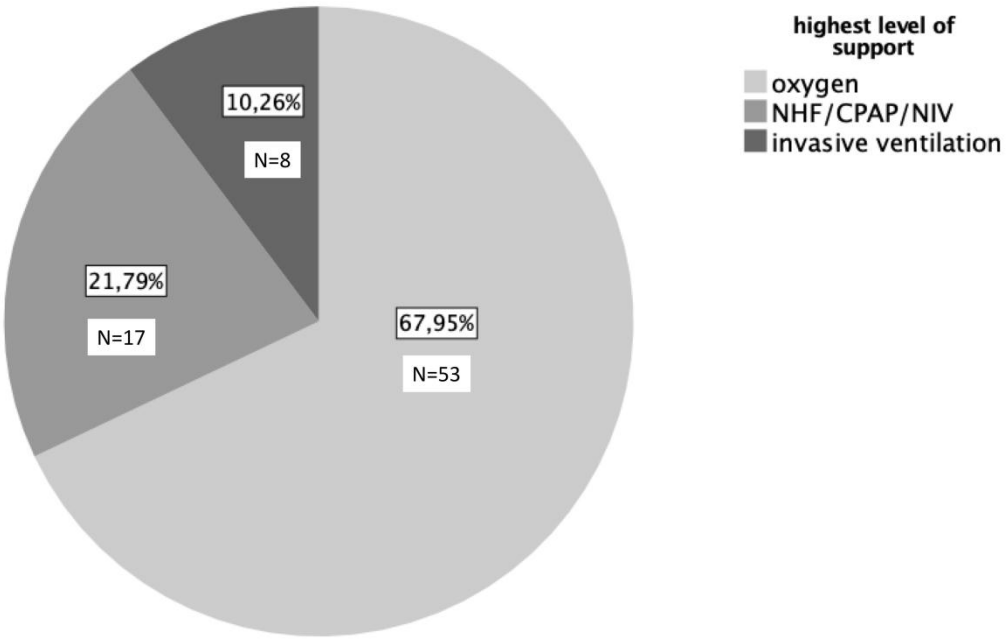
Figure 3: SaO_2 Nadir of the respective treatment groups (NHF = nasal high-flow, CPAP = continuous positive airway pressure, NIV = non-invasive ventilation).

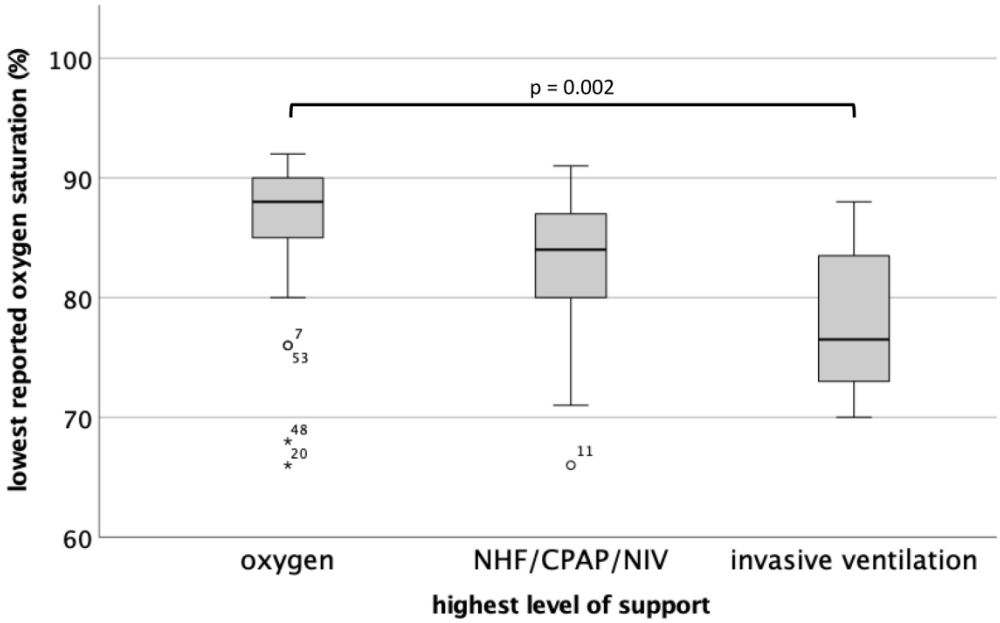
Figure 4: Lowest reported Horovitz index of the respective treatment groups (NHF = nasal high-flow, CPAP = continuous positive airway pressure, NIV = non-invasive ventilation).

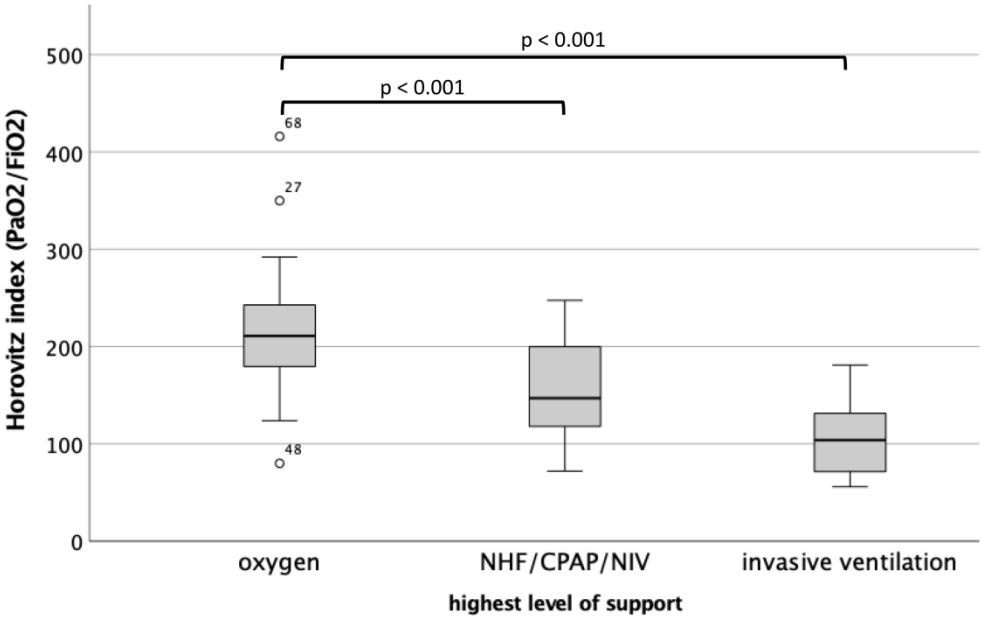
Figure 5: Lowes measured oxygen content of the respective treatment groups (NHF = nasal high-flow, CPAP = continuous positive airway pressure, NIV = non-invasive ventilation).

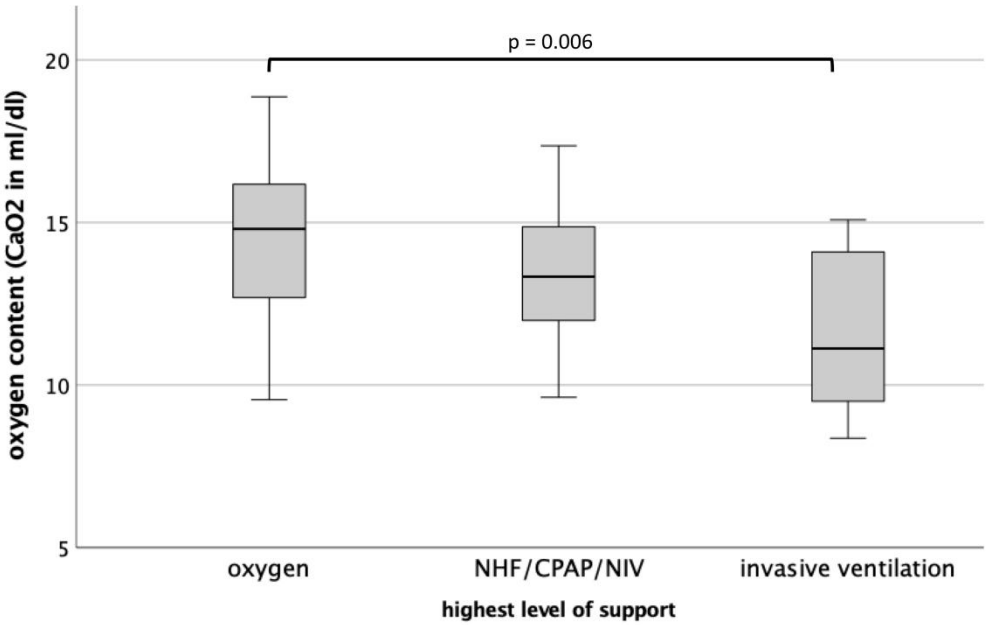
Figure 6: Outcome / respiratory support at discharge according to the maximal respiratory support received (NHF = nasal high-flow, CPAP = continuous positive airway pressure, NIV = non-invasive ventilation).

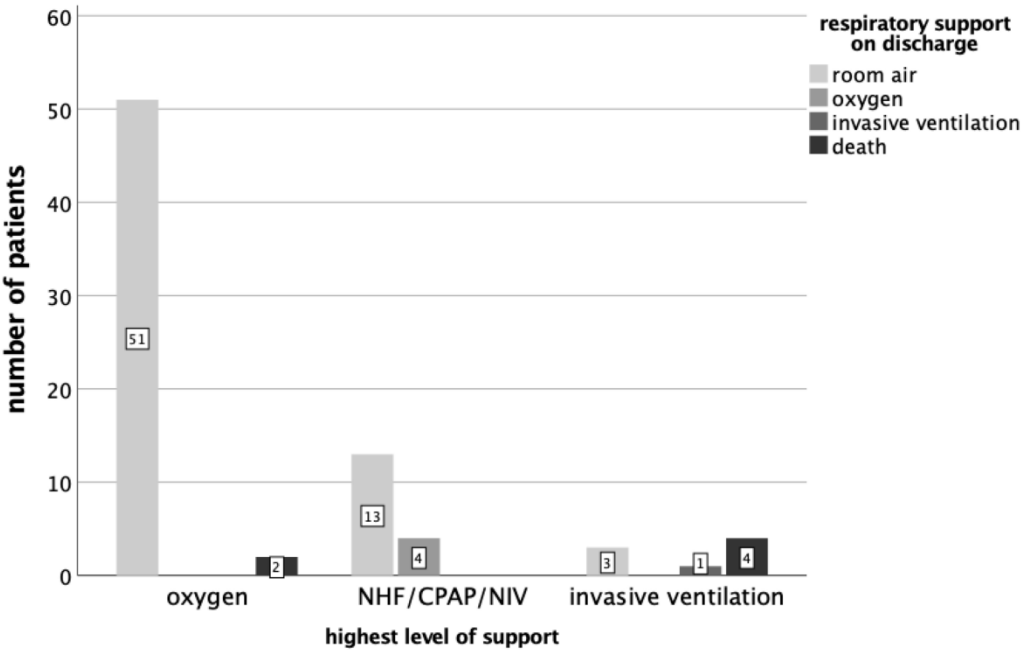

room air
supplemental oxygen
nasal-high-flow / CPAP / noninvasive ventilation
or a combination of these measures whatever
was more effective better tolerated if equally effective
invasive mechanical ventilation


highest level of support
oxygen
NHF/CPAP/NIV
invasive ventilation
10,26%
N=8
21,79%
N=17
67,95%
N=53


lowest reported oxygen saturation (%)
100
90
80
70
60
p = 0.002
7
53
48
20
11
oxygen
NHF/CPAP/NIV
invasive ventilation
highest level of support


p < 0.001
p < 0.001
Horovitz index (PaO2/FiO2)
500
400
300
200
100
0
68
27
48
oxygen
NHF/CPAP/NIV
invasive ventilation
highest level of support


p = 0.006
20
15
10
5
oxygen content (CaO2 in ml/dl)
oxygen
NHF/CPAP/NIV
invasive ventilation
highest level of support


respiratory support on discharge
room air
oxygen
invasive ventilation
death
number of patients
60
50
40
30
20
10
0
51
2
13
4
3
1
4
oxygen
NHF/CPAP/NIV
invasive ventilation
highest level of support