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Editorial Board Member of *World Journal of Nephrology*, Aristeidis Stavroulopoulos, MD, Chief Medical Officer of Pan Health Group, Ploutarchou 4, Athens 10675, Greece; Director of the Athens Kidney Institute Nephroexpert, Christovasili 3, Athens 14562, Greece

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OPINION REVIEW

Renal cell carcinoma and viral infections: A dangerous relationship?

Melissa Bersanelli, Chiara Casartelli, Sebastiano Buti, Camillo Porta

ORCID number: Melissa Bersanelli 0000-0002-6527-6281; Chiara Casartelli 0000-0001-6476-6871; Sebastiano Buti 0000-0003-0876-0226; Camillo Porta 0000-0003-2412-1563.

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Melissa Bersanelli, Chiara Casartelli, Sebastiano Buti, Medical Oncology Unit, University Hospital of Parma, Parma 43126, Italy

Melissa Bersanelli, Chiara Casartelli, Department of Medicine and Surgery, University of Parma, Parma 43126, Italy

Camillo Porta, Department of Biomedical Sciences and Human Oncology, University of Bari 'A. Moro', Bari 70121, Italy

Camillo Porta, Department of Medical Oncology, Policlinico Consorziale, Bari 70124, Italy

Corresponding author: Melissa Bersanelli, MD, Adjunct Professor, Postdoctoral Fellow, Staff Physician, Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, Parma 43126, Italy. bersamel@libero.it

Abstract

Virus-related cancers in humans are widely recognized, but in the case of renal cancer, the link with the world of viruses is not clearly established in humans, despite being known in animal biology. In the present review, we aimed to explore the literature on renal cell carcinoma (RCC) for a possible role of viruses in human RCC tumorigenesis and immune homeostasis, hypothesizing the contribution of viruses to the immunogenicity of this tumor. A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords "*virus*" or "*viruses*" or "*viral infection*" matched with ("AND") "*renal cell carcinoma*" or "*kidney cancer*" or "*renal cancer*" or "*renal carcinoma*" or "*renal tumor*" or "*RCC*". The retrieved findings evidenced two main aspects testifying to the relationship between RCC and viruses: The presence of viruses within the tumor, especially in non-clear cell RCC cases, and RCC occurrence in cases with pre-existing chronic viral infections. Some retrieved translational and clinical data suggest the possible contribution of viruses, particularly Epstein-Barr virus, to the marked immunogenicity of sarcomatoid RCC. In addition, it was revealed the possible role of endogenous retrovirus reactivation in RCC oncogenesis, introducing new fascinating hypotheses about this tumor's immunogenicity and likeliness of response to immune checkpoint inhibitors.

Key Words: Renal cell carcinoma; Renal cancer; Kidney cancer; Viruses; Viral infections; Retrotransposons

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Core Tip: An overview of the complex interplay between viral agents and renal carcinogenesis, possibly influencing the course of the disease, the tumor immune microenvironment, the production of new antigens, the host's and the tumor's immunogenicity, and, even more, the response to immune checkpoint blockade.

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INTRODUCTION

Virus-related cancers in humans are widely recognized and listed by the American Cancer Society[1]. The growing knowledge about the role of viruses as a cause of tumors has led to vaccines' development to prevent specific types of human cancers, which effectiveness is often prevented by prior exposure to the wild virus. Viruses known to be directly related to cancer are the human papillomaviruses (HPVs), leading mainly to cervix cancer and other genital or oral cancers; the Epstein-Barr virus (EBV), related to nasopharyngeal and gastric cancers, but also Burkitt and Hodgkin lymphomas; the human herpesvirus 8 (HHV8), associated with Kaposi sarcoma; the hepatitis B and C virus (HBV and HCV), provoking hepatocellular carcinoma, and even the human immunodeficiency virus (HIV) and HHV8, sometimes directly and often indirectly (through immunosuppression) related to a higher risk of developing Kaposi sarcoma, cervical cancer, tumors of the central nervous system and Hodgkin lymphoma[1].

In the case of renal cancer, the link with the world of viruses is established in animal biology, given the cause-effect relationship between the renal carcinoma of leopard frogs (*Rana pipiens*) and the Lucké tumor herpesvirus (LTHV). In 1974, the Koch-Henle postulates between LTHV and frogs' renal cancer were fulfilled, demonstrating that (1) The agent was associated with the disease; (2) The agent induced the same disease in a susceptible host; (3) The agent was isolated from the induced disease; and (4) The isolated agent was the same agent originally associated with the disease[2]. Then, in 1982, LTHV was found in the primary tumor and metastatic tumor cells in the liver, fat body, and bladder, revealing both by histopathology and electron microscopy that the virus was retained from the primary tumor to its metastatic cells[3].

Given this ancestral link, we aimed to explore the literature on human renal cancer, namely renal cell carcinoma (RCC), to verify the possible role of viruses in human RCC tumorigenesis and immune homeostasis with the host.

In addition, considering the recent advances in the field of systemic immunotherapies, with the evidence of the efficacy of anti-programmed death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and anti-CTLA-4 immune checkpoint inhibitors (ICIs) in the treatment of metastatic RCC (mRCC)[4-7], we postulated the possible contribution of viruses to the immunogenicity of this tumor. While an "inflamed" phenotype characterizes other immunogenic tumors, RCC has been defined as a tumor with a prominent dysfunctional immune cell infiltrate[8]. Its immunogenicity is not entirely attributable to an inflamed status or a high tumor mutational burden, another recently identified element responsible for immune responsiveness[9]. Indeed, enigmatic genomic clusters of RCC have been identified as good responders to ICI-based treatment regimens despite very low mutational burden and apparently non-immunogenic features. This is the case of the so-called "Cluster 7", characterized by increased expression of small nucleolar RNAs (snoRNAs), guiding chemical RNA modifications, especially SNORDs[10,11].

The possibility that the presence of viruses in cancer cells could contribute to tumor immunogenicity is already suggested by the outstanding efficacy of immune checkpoint blockade in a tumor well-known to be highly resistant to standard anticancer therapies, namely Merkel cell carcinoma (MCC)[12]. MCC is a rare and aggressive skin cancer belonging to the family of neuroendocrine tumors, characterized by small cell features non-dissimilar to that of small cell lung cancer (SCLC). Despite the well-known unresponsiveness of neuroendocrine tumors to ICIs, recently non-effortlessly introduced in SCLC's treatment algorithm, MCC is counted among the

solid tumors which the new immunotherapy has changed history. Unlike other neuroendocrine tumors, MCC is associated, in 80% of cases, with the Merkel cell polyomavirus (MCPyV). The MCPyV small T oncoprotein can inactivate p53 and contributes to metastatic progression.

Interestingly, similarly to Cluster 7 described for RCC, MCPyV-positive cases bear a much lower mutational load, notwithstanding their immunogenicity[13]. Other than an increased neoantigens' production, this immune responsiveness might be due to the viral agent's contribution to shaping a peculiar tumor immune microenvironment (TIME), likely crucial to defining tumor immunogenicity. Recent findings support this hypothesis, showing that MCPyV presence, found in 101/176 analyzed cases of MCC, was related to changes in the tumor morphology, the density of the inflammatory infiltrate, the phenotype of the neoplastic cells, and the cell composition of the tumor stroma[14]. This evidence suggests that the presence of a virus can enhance inflammation within a tumor.

Given the emerging link between inflammation and ICI responsiveness, we hypothesized that a viral agent could contribute to rendering a tumor inflamed, on the one hand shaping the TIME, and on the other hand providing a more considerable amount of non-self-antigens, finally triggering a more potent immune response. In this view, the possible involvement of viruses in RCC oncogenesis and progression becomes an issue of interest, animating our aim to collect and describe evidence supporting this hypothesis.

LITERATURE SEARCH

A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords "*virus*" or "*viruses*" or "*viral infection*" matched with ("AND") "*renal cell carcinoma*" or "*kidney cancer*" or "*renal cancer*" or "*renal carcinoma*" or "*renal tumor*" or "*RCC*". The topics included in the literature selection were viruses in RCC, and RCC in patients with chronic viral infections. The use of oncolytic viruses for therapeutic purposes in RCC was an excluded topic. Other relevant issues close to the topics of interest that emerged from the literature screening were furtherly retrieved, and relevant publications were discussed.

ISSUES EMERGED: A THREE-FACED JANUS

Our search for possible links between viruses and RCC brought out two main aspects of their relationship: The presence of viruses within the tumor, and RCC occurrence in cases with pre-existing viral infections, both events documenting a potential causality effect. In addition, our multidirectional review unrevealed the possible role of endogenous retrovirus (ERV) reactivation in RCC oncogenesis, introducing new fascinating hypotheses about this tumor's immunogenicity.

ROLE OF VIRUSES IN RCC: HISTOPATHOLOGICAL FINDINGS

The research of histopathological findings testifying the presence of viruses in RCC allowed the retrieval of five retrospective publications[15-19]. These studies identified the virus within the tumor tissue through heterogeneous assays, demonstrating the viral presence at a rate of tumor specimens ranging from 7% to 30% of the case series analyzed. Contrariwise, the same viruses were present in the respective control specimens (healthy kidney or peritumoral tissue) at a rate ranging from 0% to 4%. Table 1 summarizes the relevant data, showing HPV, EBV, and BKV polyomavirus among the viruses identified.

The role of BKV polyomavirus was already known in the field of renal transplants. About 75%-90% of healthy adults are BKV seropositive, but the virus is likely to remain non-pathogen in most cases. Immunosuppressive therapies trigger the reactivation of BKV and graft nephropathy (BKVN) in organ transplant recipients. The treatment of biopsy-proven BKVN consists of the reduction of immunosuppressive drugs. Of note, Neirynck *et al*[17] reported a case of complete remission of metastatic sites from RCC after the allograft surgical removal and immunosuppressive treatment discontinuation, suggesting the key role of BKV in a case of RCC occurred five years after renal transplant[16].

Table 1 Studies about viruses in renal cell carcinoma

Ref.	Study type	Analyzed specimens		Virus investigated	Analysis method	Positive specimens	
		No. of cases and tumor type	No. of controls and tissue type			No. of positive cases and tumor type	No. of positive controls and tissue type
Kim *et al*[18], 2005	Retrospective	73 RCC (22 clear cell; 18 papillary; 20 chromophobe; 10 sarcomatoid; 3 oncocytoma)	18 non-neoplastic kidneys	EBV	EBER-ISH and PCRs (for EBNA-1 and EBNA-3C)	5/73 (all sarcomatoid histology) (EBER-ISH)[2]; 4/73 (all sarcomatoid histology) showed amplification of EBNA-1	0/18
Neirynck *et al* [17], 2012	Case report	1 RCC[1]	1 peritumoral tissue	BKV	IHC (for SV40 T antigen)	65%-70% neoplastic cells	< 1% non-neoplastic cells
Salehipoor *et al*[19], 2012	Retrospective	49 RCC	16 non-neoplastic kidneys	HPV; EBV; BKV; JCV	Nested PCR (virus DNA)	7/49 HPV (5 clear cell; 1 chromophobe 1 mixed type) 0 EBV, BKV JCV	0/16
Bulut *et al* [16], 2013	Retrospective	50 RCC	45 non-neoplastic kidneys	BKV	Nested PCR (BKV DNA) and RT-PCR (BKV mRNA)	10/50 (Nested PCR) 8/50 (RT-PCR)	2/45 non neoplastic kidneys (nested PCR, RT-PCR)
Farhadi *et al* [20], 2014	Retrospective	122 RCC (77 conventional; 26 papillary; 14 chromophobe; 1 collecting duct; 4 unclassified)	96 peritumoral tissues, 19 non-neoplastic kidneys	HR-HPV	Nested PCR (HR-HPV DNA). IHC (for p16INK4a and L1 Capsid Protein); CSAC-ISH	37/122 (17 clear-cell; 13 papillary; 4 chromophobe; 3 unclassified) (PCR). 24/118 (IHC for p16INK4a[3]) 0/118 (IHC for L1 capsid protein); 18/122 (CSAC-ISH)	4/96 peritumoral tissues; 0/19 non-neoplastic kidneys (PCR); 16/94 peritumoral tissue (IHC for p16INK4a); 0/94 peritumoral tissue (IHC for L1 capsid protein); NA (CSAC-ISH)

[1]Allograft kidney.

[2]EBER-positive signals were located only in the tumor-infiltrating lymphocytes.

[3]Human papillomavirus capsid protein.

RCC: Renal cell carcinoma; BKV: BK virus; EBV: Epstein-Barr virus; HPV: Human papillomavirus; JCV: JC virus; HR-HPV: High-risk human papillomavirus; Nested PCR: Nested polymerase chain reaction; RT-PCR: Real-time polymerase chain reaction; IHC: Immunohistochemistry; EBER-ISH: EBV-encoded RNAs in situ hybridization; EBNA-1 and EBNA-3C: EBV-encoded nuclear antigen 1 and EBV-encoded nuclear antigen 3C; CSAC-ISH: Catalyzed signal-amplified colorimetric in situ hybridization; NA: Not available.

From a different perspective, a critical role could be attributed to immunosuppression. Renal cancer occurs more frequently in renal transplanted patients than in the general population[20]. Considering the non-negligible rate of primary RCC in the allograft and the native kidney of renal transplant recipients, a possible synergy of immunosuppressive treatments and oncogenic viruses could be hypothesized as the basis of renal cancerogenesis in these patients[21]. According to a recent meta-analysis, renal transplant recipients were found to display a higher risk of all cancers, but their standard incidence ratio (SIR) was 10.77 (95%CI: 6.40-18.12; $P < 0.001$) concerning RCC, compared to an all-cancers SIR of 2.89 (95%CI: 2.13-3.91)[22].

Besides BKV evidence in the allograft, the role of this virus might be more extensive in renal cancer, given the significant association ($P = 0.03$) found between BKV DNA positivity of specimens and histological diagnosis of RCC (but not with that of urothelial carcinoma) in a cohort including 50 RCC, 40 urothelial cancers, and 65 non-cancer controls[15]. The levels of BKV mRNA were significantly higher in the RCC samples than in the control samples ($P < 0.05$), and the presence of BKV DNA resulted

in a 5-fold increased risk of RCC[15].

The limitations of the studies analyzed, beyond the limited sample size, are represented by the scarce homogeneity of investigational techniques, in the complete lack of validated assays to assess the viral presence within the tumor tissue. In most cases, the viral nucleic acid was detected by real-time polymerase chain reaction (PCR), but immunohistochemical techniques were also explored, with non-consistent results compared to the respective PCR in the same series[19].

Interestingly, a meaningful number of virus-positive cases were found in non-clear cell RCC (nccRCC) specimens, possibly subtending a different contribution in the etiopathogenesis between clear cell RCC (ccRCC) and non-conventional histologies. In the analyzed studies, Farhadi *et al*[20] found HPV in 13 of 26 (50%) papillary RCC specimens, compared to 17/77 ccRCC (22%) in the same series; similarly, Kim *et al*[18] found 50% of RCC with sarcomatoid histology positive for EBV. While the *VHL*-driven oncogenesis is widely recognized in ccRCC[23], less is known about the chain of oncogenic events in the case of nccRCC, a heterogeneous group of tumors with different histopathological, molecular, and clinical features, which are maybe promoted by shared stimuli.

EBV in sarcomatoid RCC: Is there a virus behind immunogenicity?

Sarcomatoid RCC (sRCC) is not considered a distinct histotype: Sarcomatoid dedifferentiation is a histological feature found in any RCC subtype, conferring aggressive behavior and a lower likelihood of response to antiangiogenic therapies when compared to ccRCC[24]. sRCC is characterized by the presence of spindle-shaped cells in a varying proportion of the tumor area, accounting for a sarcoma-like aspect, engaged in epithelial-mesenchymal transition and expressing mesenchymal markers. The differential diagnosis from retroperitoneal leiomyosarcoma or liposarcoma can be challenging in locally advanced cases. Nevertheless, opposite to these latter tumors, sRCC has been recently recognized as a highly immunogenic tumor, characterized by enriched immune signatures and high levels of tumor-infiltrating lymphocytes, likely to respond to ICI more than to antiangiogenic therapy[25]. From the molecular standpoint, sRCC exhibits a lower prevalence of PBRM1 mutations and angiogenesis markers, frequent CDKN2A/B alterations, and increased PD-L1 expression[26]. These findings have been applied to molecularly stratify patients, justifying improved outcomes of sarcomatoid tumors to checkpoint blockade *vs* antiangiogenics alone in first-line trials with ICI-based combinations, recently pooled in a meta-analysis[27].

In one of the previously cited histopathological research works, among 73 RCC specimens, EBV RNA was present in only 5 samples (6.8%)[17]. Curiously, all 5 EBV-positive tumors were sRCC. Considering the sRCC subgroup of samples, EBV-positive sRCC were 5 cases out of 10 (50%). Interestingly, EBV was located exclusively in the tumor-infiltrating B lymphocytes sRCC, clearly characterizing the TIME more than the tumor cells. These findings might suggest a possible contribution of viruses, in particular EBV, to the marked immunogenicity of sRCC, furtherly reiterated by recent subgroup analyses of new ICI-based combinations[28,29].

ERV REACTIVATION FROM PROMOTING RENAL CARCINOGENESIS TO PREDICTING IMMUNE RESPONSE

Approximately 40% of the mammalian genome is constituted by retrotransposons, archaic genic sequences introduced into the eukaryotic genome during the evolution, which can copy and paste themselves into different genomic locations through reverse transcription. Retrotransposons are epigenetically silenced in most somatic tissues and usually reactivated in early embryos. Their silencing is epigenetically provided through DNA methylation, histone methylation/acetylation, and posttranscriptional regulation. Mammalian retrotransposons include non-long term repeats (non-LTR) retrotransposons and LTR retrotransposons, the latter also known as ERVs[30]. Human ERVs (hERVs) are remnants of exogenous retroviruses integrated into the primate genome over evolutionary time. Besides LTRs, hERVs share other genomic similarities to other retroviruses, like *gag*, *pro*, *pol,* and *env* genes[31]. Their sequences are not transcribed in mRNA, but they can interfere with gene expression by antisense transcription or premature transcription termination, provide new transcription start sites changing gene regulation, contain regulatory elements on target genes, mediate genomic rearrangement through nonallelic homologous recombination[30].

Recent evidence reveals hERV reactivation in RCC, with LTRs exhibiting *HIF* binding and transcriptional activity in the RCC genome[32]. Some of these *HIF*-bound LTRs may function as distal enhancers inducing the expression of genes representing potential therapeutic targets in RCC.

ERV expression was shown to correlate with histone methylation and chromatin regulation genes in multiple cancer types, including ccRCC[33]. Eventually, ERVs provide an epigenomic mechanism for recurrent transcriptional signatures observed in RCC, suggesting that this tumor's epigenomic landscape might at least partially come from viruses.

Exaptation of promoters embedded within LTRs is emerging as a recurrent element of genomic dysregulation of oncogenesis, previously demonstrated in other cancers such as Hodgkin lymphoma, melanoma, and large B cell lymphoma. Recent research reported the first description of retroviral LTR exaptation in RCC, with distinct mechanisms from previous reports about this phenomenon[32]. Further evidence was provided on pan-cancer datasets by the Cancer Genome Atlas (TCGA): Using a previously compilated database of 3173 intact, full-length ERV sequences, Smith and co-investigators designed a computational workflow for identifying the expression of specific ERVs from RNA-sequencing and quantified ERVs expression in different tumors[31]. They evidenced that ccRCC contained the most significant number of prognostic ERVs among all cancer types encompassed, with shorter survival in patients with greater mean ERV expression (testifying a negative prognostic value).

As a further crucial step in this field, ERVs in RCC have recently been demonstrated predicting immunotherapy response in ccRCC, as contemporarily reported in 2018 by two independent research groups[31,33].

Smith *et al*[32] identified a signature marking anti-PD-1 responsiveness associated with hERV expression, while a signature for non-responder tumors was negatively associated with hERV expression[31]. They explored the mechanisms by which hERV expression in tumor cells influenced the TIME in RCC, discovering immune stimulation evidence through RIG-I-like signaling of the hERV-induced adaptive immune response through B cell activation. Also, they showed that hERVs mediated the tumor-specific presentation of targetable viral epitopes, possibly adding a trigger to the antitumor response. On the other hand, ERV proteins were already known to be expressed and immunogenic in ccRCC[34-36].

Similarly, Panda *et al*[34] identified 20 potentially immunogenic ERV (πERVs) in ccRCC in TCGA dataset, demonstrating that πERV-high ccRCC tumors had an increased immune infiltration checkpoint pathway upregulation and higher CD8+ T cell fraction in infiltrating immune cells compared to πERV-low ccRCC tumors[33]. Moreover, πERV-high ccRCC tumors were enriched in *BAP1* mutations. As a further step, they demonstrated that the RNA level of specific ERVs (*ERV3-2*) was an excellent predictor of response to immune checkpoint blockade, as statistically significantly higher in tumors from responders compared with tumors from non-responders patients with metastatic ccRCC treated with single-agent PD-1/PD-L1 antibody[33]. This evidence is significant in light of the confirmed poor prognostic significance of πERV-high and πERV-intermediate expression, as verified by the same authors. The validation sample was represented by πERV-high and πERV-intermediate ccRCC patients treated with standard therapy, showing significantly shorter overall survival (OS) than patients with πERV-low tumors [OS, hazard ration (HR) 1.44 (95%CI: 1.06-1.97), $P = 0.02$][33].

These findings suggested ERVs' striking relevance on the immune checkpoint activation in ccRCC, potentially configuring a new biomarker of inflamed tumors, more likely to respond to ICI immunotherapy.

RCC IN PATIENTS WITH CHRONIC VIRAL INFECTIONS: IS THERE ANY CAUSE-OUTCOME RELATIONSHIP?

Chronic viral infections are often subtended by a dysfunctional immune response, possibly conferring a persistently inflamed status to the host, likely dominated by T-cells exhaustion. Several authors have reported the increased incidence of malignancies in patients with chronic viral infections, and some consistent literature also emerged in the field of renal cancer (Table 2)[37-43].

Chronic HCV infection seems to confer a risk for the development of RCC, according to a cohort study of 67063 HCV-tested patients, among whom RCC was diagnosed in 0.6% of HCV-positive *vs* 0.3% of HCV-negative patients. The univariate HR for RCC among HCV patients was 2.20 (95%CI: 1.32-3.67; $P = 0.0025$). In a

Table 2 Studies reporting the relationship between chronic viral infections and the occurrence of renal cell carcinoma

Ref.	Study type	Type of chronic viral infection	Study population	RCC histology	Mean age (yr)	Aim	Main results/conclusions
Gaughan *et al* [43], 2008	Case series	HIV infection	9 HIV-associated RCC[1]	2 papillary, 1 collecting duct, 6 clear cell	48	To describe the risk factors, clinical findings, pathology, and response to therapy in RCC patients infected with HIV	The clinical presentation and behavior of RCC in patients with HIV infection appeared similar to that of the HIV-negative population and that chronic immunosuppression plays a lesser role than age and exposure to risk factors
Gordon *et al* [38], 2010	Retrospective study	HCV infection	67063 HCV-tested patients: 3057 HCV+ and 64006 HCV-	17 RCC HCV+: 8 clear cell, 6 papillary, 2 mixed clear cell/papillary, 1 undifferentiated/other; 117 HCV-: 92 clear cell, 43 papillary, 9 mixed clear cell/papillary, 26 undifferentiated/other	54 in HCV+, 63 in HCV-	To determine whether HCV infection confers an increased risk for developing RCC	RCC was diagnosed in 0.6% (17/3057) of HCV+ and 0.3% (117/64006) of HCV- patients. HCV infection confers a risk for the development of RCC: Overall HR for RCC among HCV patients 1.77 (95% confidence interval, 1.05-2.98; $P = 0.0313$)
Wiwanitkit [42], 2011	Bioinformatics analysis	HCV infection	NA	NA	NA	To assess the cause–outcome relationship between HCV infection and RCC using the bioinformatics network analysis technique	There might be a cause–outcome relationship between HCV infection and RCC *via* NY-REN-54 (the only one common protein)
Gonzalez *et al* [39], 2015	Prospective study	HCV infection	140 RCC and 100 colon cancer patients (control)	NA	56.7 in RCC patients with viremia, 61.8 in aviremic patients	To determine whether chronic HCV is associated with an increased risk of RCC	11/140 RCC and 1/100 colon cancer patients were HCAB+. Of the HCAB+ patients, 9/11 RCC and 0/1 controls had detectable HCV RNA. In the multivariable logistic regression analysis, being HCV RNA positive was a significant risk factor for RCC ($P = 0.043$)
Wijarnpreecha *et al*[40], 2016	Systematic review and meta-analysis	HCV infection	196826 patients from 7 observational studies (4 cohort and 3 case-control studies). Individuals without HCV infection were used as comparators in cohort studies, individuals without RCC as comparators in the cross-sectional and case-control studies	NA	NA[2]	To assess the risk of RCC in patients with HCV infection	Significantly increased risk of RCC in HCC+ with the pooled risk ratio of 1.86 (95%CI: 1.11-3.11)
Ong *et al*[44], 2016	Case series	HIV infection	7 HIV-associated RCC[1]	5 clear cell, 1 papillary, 1 unknown	56	To report presentation, management and outcomes of RCC patients with HIV infection	RCC patients with HIV infection should be offered all treatment options in the same manner as the general population
Tsimafeyeu *et al* [41], 2020	Retrospective study	HCV infection	44 mRCC patients: 22 HCV+, 22 HCV-	Clear cell	62 in mRCC HCV+, 63 in mRCC HCV-	To evaluate Nivolumab efficacy and safety in mRCC patients with or without chronic HCV infection (OS primary endpoint, PFS, ORR and rate of grade 3–4 adverse events secondary endpoints)	HCV-infected patients had significantly longer OS (27.5 *vs* 21.7, $P = 0.005$) and PFS (7.5 *vs* 4.9, $P = 0.013$), no difference in ORR. Grade 3–4 adverse events were observed in 5 (23%) HCV+ patients and in 3 (14%) HCV- patients

[1]Human immunodeficiency virus infection before renal cell carcinoma (RCC) diagnosis.
[2]Mean age not specified, but hepatitis C virus (HCV)+ RCC patients were significantly younger than HCV-RCC patients.
HCV: Hepatitis C virus; RCC: Renal cell carcinoma; mRCC: Metastatic renal cell carcinoma; HR: Hazard ratio; NA: Not available; HCAB: Hepatitis C antibody; RNA: Ribonucleic acid; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; HIV: Human immunodeficiency virus.

multivariate model that included the risk factors age, race, gender, and chronic kidney disease, the overall HR for RCC among HCV patients was 1.77 (95%CI: 1.05-2.98; P = 0.0313)[37].

In another report, RCC patients were shown to have a higher rate of hepatitis C antibody positivity (11/140, 8%) than colon cancer patients (1/100, 1%, P = 0.01), viremic RCC patients were significantly younger than RCC patients who were HCV RNA negative (P = 0.013)[38].

A meta-analysis of seven observational studies including 196826 patients, the risk of RCC in HCV patients was found to increase with a pooled risk ratio (RR) of 1.86 (95%CI: 1.11-3.11). Nevertheless, the association between RCC and HCV was marginally insignificant after a sensitivity analysis limited only to studies with adjusted analysis, with a pooled RR of 1.50 (95%CI: 0.93-2.42)[39].

In HIV infection, AIDS-related immunosuppression could play the leading role in promoting oncogenic events instead of the viral infection itself. The literature simply included RCC in the expanding array of non-AIDS-defining malignancies that develop during HIV infection[42,43].

On the other hand, subtending viral infections could represent the epiphenomenon of a dysfunctional immune status, maybe more likely to benefit from immune checkpoint blockade[44]. In a matched cohort study, data were collected from 174 patients with metastatic ccRCC, chronic HCV infection (case study group), no evidence of other malignancy or cirrhosis, and had received nivolumab as systemic anticancer treatment[39]. HCV-infected patients had significantly longer OS and progression-free survival (PFS). Median OS was 27.5 (95%CI: 25.3–29.7) and 21.7 (20.3–23.1) in study and control groups, respectively (P = 0.005). Median PFS was 7.5 (5.7–9.3) and 4.9 (4–5.8) (P = 0.013). Despite no differences in objective response rate between groups, patients with HCV had significantly more durable responses (P = 0.01). Such findings are undoubtedly suggestive but still largely insufficient to draw a causality relationship between chronic viral infections and immunogenicity.

The report of acute viral infections triggering an anticancer immune response in patients with solid and hematological malignancies is rather than new. From the first observation by William Coley that non-self-agents can trigger antitumor immune reactivity to the recent findings by our research group about influenza infection in advanced cancer patients treated with ICI immunotherapy, the literature emphasizes the role of extrinsic immune stimulation in modulating the immune reactivity and also the efficacy of inhibitory molecules targeting immune checkpoints[45,46]. Even SARS-CoV-2 was reported as able to exert an abscopal antitumor effect in solid tumors: Cases of partial or complete remission during COVID-19 have been reported in

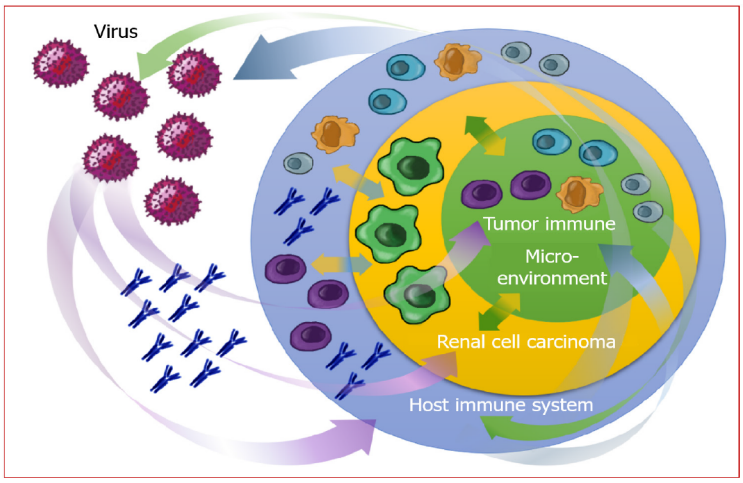

Figure 1 The crosstalk between the virus, the host, and the tumor is likely to influence the mutual interplay between the tumor itself, its immune microenvironment, and the host with renal cell carcinoma.

patients with melanoma and lymphomas without any anticancer treatment, in the latter cases likely due to a direct oncolytic effect on tumor cells[47-49].

Compared to cancer diagnosis in chronically infected individuals, likely driven by immunosuppression and immune exhaustion[50], the occurrence of viral infections in patients with cancer represents an opposite setting. In this case, the encounter with viral antigens could contribute, as a potent exogenous immunological stimulus, to shift the balance between tolerance and activation, likely favorably influencing the TIME and the complex relationships between the tumor and the host (Figure 1).

The possible contribution of viruses in kidney cancers with variant histology

For completeness, state-of-the-art about viruses and kidney cancer also included evidence about collecting duct carcinoma (CDC), rare variant histology with poor prognosis, and challenging therapy[51]. Notably, BKV polyomavirus was reported in the literature as linked to CDC in transplant recipients, again highlighting the role of immunosuppression as the playing field for virus-associated carcinogenesis[52,53].

CONCLUSION

The evidence presented above is a tickling proof-of-concept subtending the possibility to add a dowel for the prediction of cancer patients' outcome to immune checkpoint therapy and even more suggests exploiting the immunogenic potential of viruses for therapeutic purposes in the context of anticancer immunotherapy for RCC. Although manipulating viruses could sound like a dangerous game just in the context of the pandemic currently ongoing, teased by striking findings from this preliminary translational research, the authors of the present opinion review still consider the possibility that dangerous relationships may be the most immunogenic, at least in the context of RCC.

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REVIEW

Literature review of the mechanisms of acute kidney injury secondary to acute liver injury

Esther Platt, Enriko Klootwijk, Alan Salama, Brian Davidson, Francis Robertson

ORCID number: Esther Platt 0000-0003-3248-2414; Enriko Klootwijk 0000-0002-7447-4167; Alan Salama 0000-0002-9255-9092; Brian Davidson 0000-0002-9152-5907; Francis Robertson 0000-0001-5016-5944.

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Esther Platt, Brian Davidson, Francis Robertson, Division of Surgery and Interventional Science, University College London, London NW3 2QG, United Kingdom

Enriko Klootwijk, Alan Salama, Department of Renal Medicine, University College London, London NW3 2PF, United Kingdom

Corresponding author: Esther Platt, FRCS (Gen Surg), MA, MBBS, Surgeon, Department of Surgery and Interventional Science, University College London, Royal Free Campus, University College London, No. 9 Floor Royal Free Hospital, Pond Street, London NW3 2QG, United Kingdom. esther.platt.20@ucl.ac.uk

Abstract

People exposed to liver ischaemia reperfusion (IR) injury often develop acute kidney injury and the combination is associated with significant morbidity and mortality. Molecular mediators released by the liver in response to IR injury are the likely cause of acute kidney injury (AKI) in this setting, but the mediators have not yet been identified. Identifying the mechanism of injury will allow the identification of therapeutic targets which may modulate both liver IR injury and AKI following liver IR injury.

Key Words: Liver failure; Liver transplantation; Ischaemia-reperfusion injury; Acute kidney injury; Liver

Core Tip: Acute kidney injury (AKI) following liver injury is likely to be mediated by circulating molecules. Further investigation is required to identify therapeutic targets to modify liver injury and AKI and reduce the morbidity and mortality associated with this condition.

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L-Editor: A
P-Editor: Wu YXJ

INTRODUCTION

Ischaemia reperfusion (IR) injury is typified by initial hypoperfusion and inadequate oxygen supply to end organs. This is followed by a secondary inflammatory reperfusion injury which impacts organ function and may affect distant organs[1]. IR injury can occur as part of a global hypoperfusion phenomenon such as that seen in trauma, sepsis and haemorrhage[1-4]. IR injury may also represent a local issue of poor perfusion that primarily affects a single organ or body region.

In the clinical setting, liver IR injury is commonly seen following liver resection and liver transplantation (LT)[5]. Liver IR injury following transplant is associated with major complications related to the liver injury, including early allograft dysfunction, primary nonfunction and ischaemic-type biliary complications[6,7]. In addition to liver specific outcomes, secondary organ injury may occur, which also increases the morbidity and mortality of liver transplantation and resection. Acute kidney injury (AKI) in particular, is very strongly linked to liver IR injury following liver transplantation[8,9]. 40% of liver transplant patients develop AKI, and 7% require renal replacement therapy (RRT)[10]. These patients have an increased mortality with a mortality odds ratio of 2.96, increasing to 8.15 in severe AKI with RRT requirement [10]. AKI post LT is also associated with graft failure, prolonged intensive care unit stay, delay to hospital discharge and subsequent development of chronic kidney disease (CKD)[10-14]. Post-transplant CKD is independently associated with an increase in late mortality and cardiovascular events[11].

Supportive treatment of AKI with renal replacement therapy does not resolve the excess mortality and poor outcomes associated with this condition[15,16]. This may be because AKI needing RRT is a marker of a more global injury affecting the function and viability of multiple organs[15].

There are no specific drug therapies that reverse AKI or block its development. This may in part be related to the overall lack of understanding of the mechanisms underlying the development of AKI following liver IR injury. An improved understanding of the underlying mechanisms of injury is likely to facilitate development of new strategies to avoid and downregulate injury, provide targets for new therapies and improve clinical outcomes post liver transplantation and resection. In the context of liver transplantation, effective therapeutic interventions for both liver IR injury and AKI would also allow expansion of the donor organ pool by inclusion of more marginal grafts, which are more susceptible to IR injury.

In recent years, the indications for liver transplantation have been expanded to include the treatment of primary hepatocellular carcinoma and carefully selected patient groups with some forms of metastatic disease[17,18]. Meeting this potential enormous expansion in transplant demand would necessitate the routine use of marginal grafts. Marginal grafts include those with background hepatic steatosis, grafts from donors following cardiac death and prolonged graft ischaemia times[19, 20]. They are especially susceptible to IR injury and are associated with an increased incidence of AKI and higher mortality[19]. The lack of therapeutic interventions which either provide recipient renal protection from significant liver IR injury or downregulate liver IR injury continues to limit the use of marginal grafts in liver transplantation[21]. Addressing these issues has the potential to revolutionise the use of marginal grafts and meet the current deficit between graft supply and demand.

The clinical importance of both liver IR injury and resultant AKI is clear. Several recent reviews have addressed either mechanisms of liver IR injury or clinical aspects of liver IR injury and AKI. However, no prior review has explored the experimental and clinical evidence for the link between liver IR injury and AKI and the mechanisms mediating AKI after liver transplantation. With a recent expansion in the primary literature on this topic, we believe a review is now warranted to crystalise current understanding, identify unanswered questions and to prioritise future research. In this review we will pull together current evidence for the molecular and physiological mechanisms of kidney injury following liver IR injury.

Figure 1 provides a schematic summary of the evidence for pathways mediating liver IR injury leading to kidney injury that will be discussed throughout this review.

RENAL INJURY IS DIRECTLY LINKED TO LIVER IR INJURY AND OCCURS EARLY FOLLOWING LIVER REPERFUSION

The link between liver IR injury and AKI in liver transplantation has been well established in multiple analyses. A retrospective study of 116 patients undergoing

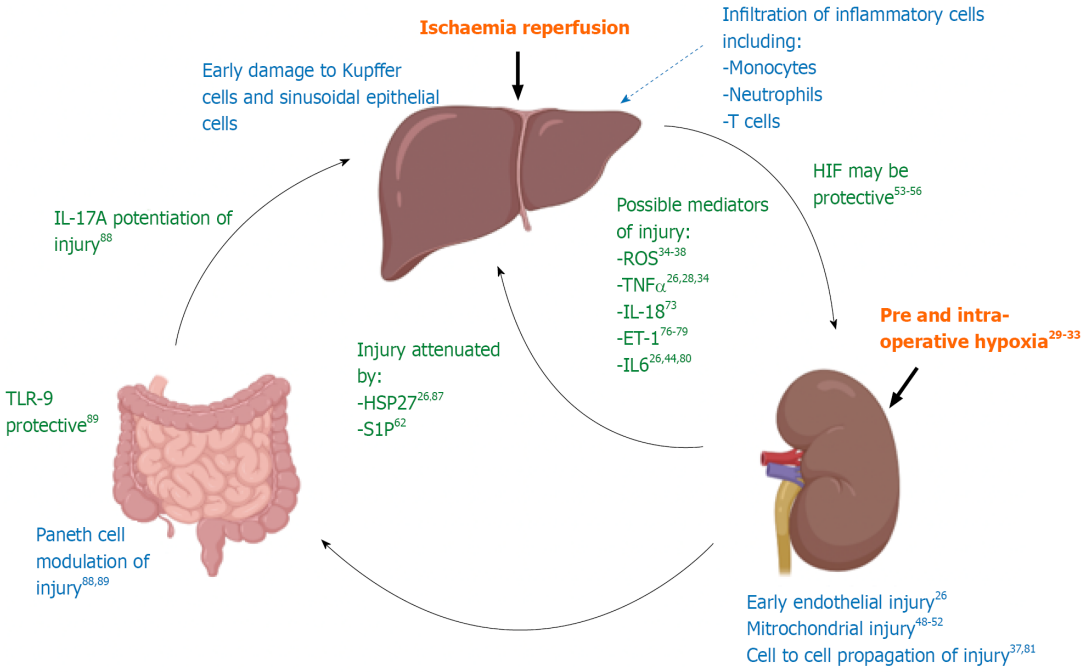

Figure 1 Schematic representation of current evidence to support the mechanistic link between liver IR injury and resultant kidney injury. The evidence for the possible mediators of injury detailed in this diagram will be discussed in more detail in the text of this review. A summary of the major studies discussed in this review can also be found in Supplementary Table 1.

deceased donor liver transplant in our unit identified post transplant serum AST/ALT as the only independent predictor of early post-operative AKI[8], a finding also demonstrated by Jochmans *et al*[9] in their prospective analysis of 88 patients who received livers from donation after brainstem death donors. These clinical data are supported by findings from rodent models of liver IR injury, typified by Lee *et al*[22], who demonstrated a direct relationship between plasma ALT and severity of AKI at 4 h and 24 h in a mouse model of partial hepatic ischaemia (right lobe of liver spared).

Renal injury is not only linked to liver ischaemia injury, but occurs promptly after reperfusion, both in the clinical setting and in animal models. In human liver transplantation, Neutrophil Gelatinase Associated Lipocalin (NGAL), a biomarker of early renal injury, is elevated in urine as early as two hours post reperfusion[23].

In rodent models of liver IR injury, histologically demonstrable renal injury is evident two to four hours post liver reperfusion[24]. Key histological features of renal injury in this context include hyperplasia and necrosis of the juxta-glomerular apparatus, endothelial apoptosis and multifocal acute tubular injury with disruption of F-actin cytoskeletal architecture, leading to S3 segment proximal tubule necrosis, focal tubular simplification (loss of brush border with cellular flattening), cytoplasmic vacuolisation, dilated tubular lumina and focal granular bile/haem casts[22,25,26], as depicted in Figure 2. A standardised grading system for severity of renal injury in rodent models of liver IR injury and AKI, including stratification of histological findings that are more associated with severe AKI, has not yet been developed. Additionally, both the sequence of injury and time frame for improvement in histological changes has not been fully defined.

The development of renal injury within a few hours of liver IR injury in both human clinical and animal experimental data hints at direct transmission of injury from liver to kidney. Liver derived molecules, washed out of the liver during organ reperfusion, may be critical mediators of AKI in this context. As the first cells to encounter haematologically transmitted mediators of injury, endothelial cells might be expected to bear the initial brunt of injury. In rodent models of liver IR injury and AKI, renal endothelial injury predominates[25], supporting this hypothesis. Human histological data is sparse and so we await verification that the rodent pattern of renal injury occurs in the human setting. An *in vitro* human model that permitted demonstration of haematological transmission of liver IR injury to the kidney would also be of huge experimental benefit. This has yet to be developed.

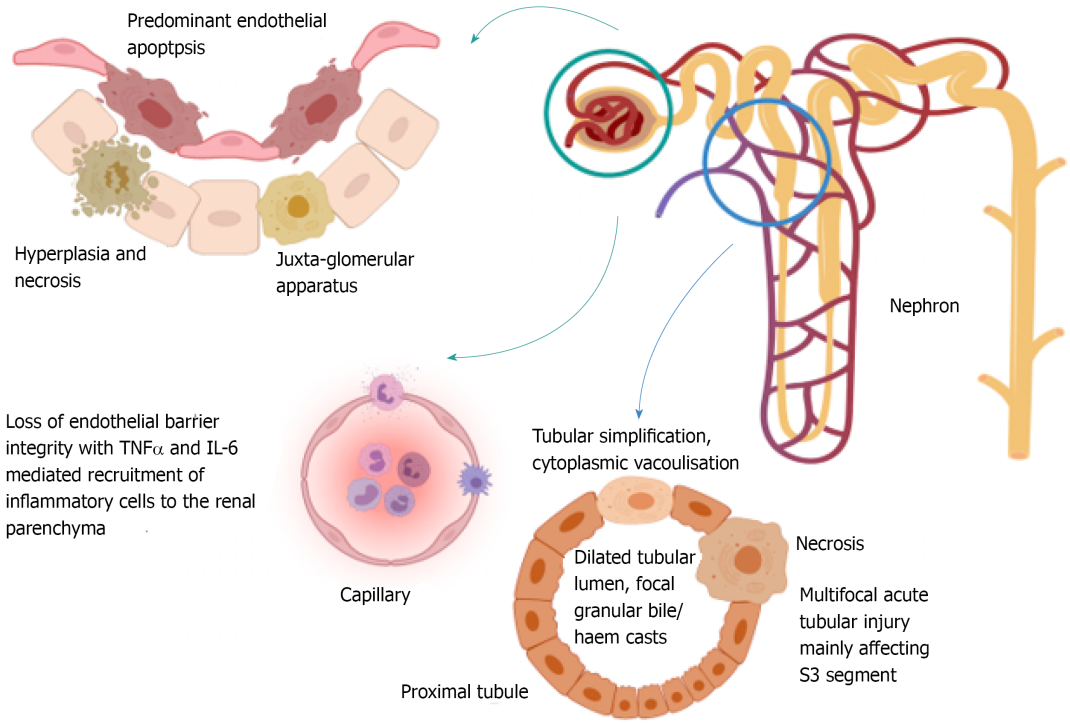

Figure 2 Diagrammatic representation of the current understanding of histological changes within the kidney that accompany acute kidney injury following liver ischaemia reperfusion injury. These data are obtained from animal studies. To date no objective grading system for histological severity of injury has been developed which means that only limited comparison of injury severity between studies is possible. Development of an objective scoring system across the first 48 h of renal injury would be of great benefit in this field of research.

SETTING THE STAGE FOR RENAL INJURY POST LIVER IR INJURY: PRE-OPERATIVE AND INTRA-OPERATIVE PROMOTERS OF INJURY

Whilst molecular mediators released by the liver following IR injury are likely to play a key role in renal injury, evidence suggests that renal injury following liver IR injury is a two-hit phenomenon. Both pre-existing renal abnormalities and intra-operative fluctuations in arterial oxygen concentrations may render the kidney relatively chronically hypoxic and prime it for further damage by circulating mediators of reperfusion injury[27,28]. This seems to be a different phenomenon from controlled ischaemic pre-conditioning which appears to reduce liver and renal injury in a mouse model of liver IR (unpublished data).

Background liver cirrhosis is associated with chronic renal injury and poor renal perfusion which may predispose the kidney to further injury

Renal biopsies performed in the context of cirrhosis demonstrate pathological changes in the kidney, mainly centred around the glomerulus, in 70% of patients. These include mesangial expansion, thickening of capillary walls, a mild increase in the number and size of endothelial and epithelial cells and IgA deposition[28]. These changes may reflect the chronic release of pro-inflammatory mediators from ongoing chronic inflammation in the liver.

Cirrhosis also reduces systemic vascular resistance[28]. When the increased cardiac output can no longer compensate for the reduction in systemic resistance there is arterial hypoperfusion. This leads to activation of vasoconstrictor systems, including the sympathetic nervous system and the renin: Angiotensin: Aldosterone axis with hypersecretion of Anti-Diuretic Hormone. The net result is Na^+ and water retention but with hypovolaemia, renal arterial hypoperfusion and renal vasoconstriction leading to renal failure[28]. This pre-existing inflammatory and hypoxic injury may prime the kidney for further injury during liver transplantation.

There may be intra-operative fluctuations in renal perfusion during liver transplantation leading to a primary kidney insult before liver IR injury

Liver transplantation results in huge fluctuations in mean arterial pressure (MAP) but there is conflicting evidence for an association between MAP and AKI. In a

retrospective study of patients undergoing living donor liver transplantation, severe hypotension (MAP < 40) in the recipient for even less than 10 min was independently related to development of post-operative AKI[29]. In a rat model of liver transplantation with doppler assessment of renal artery flow, Kong *et al*[24] noted increased renal resistive index (RI) during the anhepatic phase and reduced renal RI (compared to background) immediately post reperfusion (although this normalised within 30 min). The findings indicate maldistribution of blood flow to the kidney during the anhepatic phase with increased renal vein pressure secondary to IVC clamping serving to increase renal RI and reduce renal perfusion. Reperfusion is associated with reduced renal arteriolar tone, which the authors suggest may be due to an imbalance between vasoconstrictive and vasodilative factors, disturbing the adaptive capacity of the renal vasculature (not measured in this study). RI did not correlate with the development of AKI at 30 min and 2 h post operatively with this animal model and so RI and renal perfusion may not be the most important factors influencing AKI development.

Kandil *et al*[30] demonstrated similar fluctuations in MAP between the anhepatic and post reperfusion phases of human liver transplantation, although these were not statistically evaluated. In this double-blinded trial, patients were randomised to intra- and post-operative terlipressin infusion or placebo. Terlipressin induces systemic arterial vasoconstriction with renal sparing. It was hypothesised that systemic vascular resistance support with terlipressin would improve renal perfusion and reduce post-operative renal injury. However, the authors demonstrated equivalent incidence of AKI in both the terlipressin and placebo groups which was subsequently supported by evidence from a meta-analysis on the subject[31]. Other causes of fluctuating MAP that may contribute to renal hypoperfusion in addition to systemic vascular resistance were not evaluated in this study.

Thus, whilst a short period of significant hypotension may promote the development of post-operative AKI, the relationship between renal perfusion and subsequent development of AKI requires further investigation and so far evidence suggests that renal perfusion may be less important than circulating factors for the development of AKI following liver IR injury.

Renal hypoxia in liver transplantation may promote development of liver IR induced AKI

In human liver transplantation, low arterial oxygen concentration at 5 min post reperfusion is independently associated with development of AKI (this study included assessment of hypotension)[32]. Arterial hypoxia may result in renal hypoxia, causing primary renal injury. However, only absolute oxygen concentrations rather than relative changes were evaluated in this study. It may be that the relative drop in arterial oxygen concentration at reperfusion reflects the degree of ischaemia and oxygen debt within the donor graft, with higher oxygen tension gradients between the recipient vasculature and more profoundly ischaemic grafts (although this has not yet been evaluated experimentally). Post reperfusion arterial hypoxiaemia may therefore be a surrogate measure of liver IR injury, rather than arterial hypoxia providing a direct contribution to renal injury.

That said, the kidney is highly susceptible to hypoxic injury. Under normal physiological conditions, 80% of the renal oxygen requirement is used to drive the Na^+/K^+/ATPase pump in the proximal tubule. To meet these demands, the kidney is rich in vascular endothelium and has an excellent blood supply[27]. This in turn may make the kidney particularly vulnerable to circulating cytokines which trigger endothelial injury, especially in the situation of mass dilation of capillary beds as can occur during reperfusion secondary to the imbalance of vasodilatory and vasoconstrictive factors discussed in section 1[24].

Put together, the data suggest that the kidney is vulnerable to hypoxic injury and that post reperfusion arterial hypoxia is linked to the severity of renal injury following liver IR injury. Clinically it would be difficult to tease out the relative contributions to AKI from primary renal hypoxia and the more severe liver IR injury that is suggested by arterial hypoxia. Use of in vitro human models of injury where renal hypoxia can be controlled independently of liver IR injury would help to resolve this question. Such models have not yet been reported in the literature.

WHAT ARE THE MOLECULAR MEDIATORS OF RENAL INJURY FOLLOWING LIVER IR INJURY?

Many inflammatory mediators have been implicated in liver IR injury and/or resultant AKI. The discussion below will focus on the major molecules (both injurious and protective) of current investigative interest and draw together the discussion in the literature to provide an overview of current understanding.

Reactive oxygen species may be critical in the early transmission of injury to the kidney following liver IR injury

Reactive oxygen species may originate from the liver and circulate to the kidney[33] or arise primarily in the kidney, where they may be generated following endothelial injury and poor capillary perfusion with resultant relative hypoxia. Hydrogen peroxide (H_2O_2), superoxide anion and hydroxyl radical have all been implicated in this process[34]. Oxidative stress is thought to be the main mediator of primary tissue damage during the first four hours of reperfusion. In a rat model of liver transplantation, oxidative stress in the kidney was shown to increase roughly 2.5 fold and peak at 8 h post reperfusion (measured as H_2O_2 normalised to sham laparotomy) [35,36]. Reactive oxygen species (ROS) bind to critical cellular biomolecules including proteins, DNA and membrane lipids, and cause oxidative modification, with resultant tissue injury[37].

The detrimental action of ROS may be potentiated by ongoing release of ROS from infiltrating inflammatory cells in the later phase of liver reperfusion injury. Activated neutrophils and macrophages release ROS, including superoxide anions and hydroxyl radicals which promote cell death[33]. However, in the longer term ROS may also be regenerative; late neutrophil release of ROS may play a key role in the development of reparative macrophages to orchestrate liver tissue repair following liver injury[38].

Albumin, which acts as a free radical scavenger and endothelium stabiliser is protective in this clinical context; low circulating levels of albumin as found in advanced liver disease are associated with an increased incidence of AKI post liver transplantation[39]. Likewise, administration of various antioxidants and free radical scavengers have been shown to reduce markers of renal oxidative stress and attenuate injury post liver IR in different animal models[40,41]. Iron free radicals may play an important role in the generation of ROS and ferroptosis[42]. Desferrioxamine (DFO), the iron chelator, blocks oxygen free radical production and lipid peroxidation. Administration of DFO was found to attenuate liver IR injury in pigs and was associated with no or subtle tubular injury. Pigs exposed to liver IR injury without DFO demonstrated extensive necrosis of tubular epithelial cells and dilatation of tubular lumina, indicating severe renal injury[43]. Notably the circulating serum iron concentration was not different between DFO-treated animals and controls, implying a specific function of DFO with reactive iron species. It is not known whether this function is separate from the iron binding capacity of DFO.

These findings have not been successfully translated to the clinical setting. Administration of N-acetylcysteine during major liver surgery, including transplantation, is associated with a modest improvement in transaminase levels without impacting either AKI, graft or patient survival[44-46]. Thus whilst ROS are likely to be critical in the early mediation of AKI following liver IR injury, further work is required to identify clinically useful targets that will downregulate injury following liver transplantation and hepatic resection.

Mitochondria are vulnerable to injury and may be the main site of ROS production following liver IR injury

Mitochondria are believed to play a key role in the pathogenesis of renal injury following a variety of insults, with reduced biogenesis (generation of new mitochondria in response to increased energy demand, mitochondrial stress or damage) resulting in attenuated capacity to meet the energy demand and ATP production necessary for injured cells. Mitochondria are also the key site of ROS generation within the cell[35] and ironically mitochondrial injury may also be mediated by ROS[47] or iron species, with DFO demonstrated to attenuate mitochondrial injury in other settings[48]. In a rat model of liver transplantation and AKI, Liu *et al*[49] demonstrated a reduction in key proteins (and mRNA) involved in or regulating mitochondrial biogenesis, fission and fusion including AS-B, ND3, PGC-1α, Tfam, Drp-1 and Fis-1. Mediators of mitophagy and autophagy (PINK-1 and LC3) were also upregulated with AKI in this model. Stimulation of mitochondrial

biogenesis has also been demonstrated to reduce renal IR injury[50,51].

Taken together, the data on ROS suggest local involvement in the pathogenesis of both liver IR injury and subsequent renal injury, with mitochondrial involvement in both the generation of ROS and mediation of ROS effects. However, demonstration of direct haematological transmission of ROS from liver to kidney producing subsequent kidney injury has not been demonstrated.

Hypoxia Inducible Factors may be protective following liver IR injury

Hypoxia inducible factor 1 (HIF-1) is an important mediator of the cellular transcriptional response to hypoxia and plays a key role in the response to liver IR injury. HIF-1 comprises an oxygen destructible alpha subunit and an oxygen-indestructible beta subunit, which dimerise under hypoxic conditions.

HIF-1α silencing pre-injury promotes cellular damage in response to hypoxia, leading to increased serum levels of glucose, lipids, ALT and AST[52]. Conversely, pre-injury activation of HIF-1α attenuates hepatic IR injury by attenuating liver necrosis, the inflammatory response, oxidative stress and apoptosis[53]. HIF-1α stability is partially mediated by the oxygen sensing prolyl hydroxylase domain 1 (PHD1), which under normoxic conditions tags HIF-1α for proteosomal degradation. Interestingly PHD1 function is repressed by miR122, a target gene of HIF-1α, which is almost exclusively expressed in hepatocytes[54]. By this mechanism, HIF-1α enhances HIF mediated cellular responses through PHD1 repression.

Downstream actions of HIF-1 may be key in the attenuation of liver IR injury with subsequent downregulation of AKI but the exact involvement and mechanisms remain unclear. It may be that such effects are mediated by other microRNAs involved in the transcriptional response to HIF-1[54]. The concentration of microRNAs from donor liver perfusate (but not tissue) at the end of cold ischaemia has been linked to elevated AST and graft long term survival[56]. If present in perfusate, these microRNAs may be produced by damaged liver cells that are being flushed out of the liver. The role of such microRNAs in the mediation of kidney injury requires further investigation.

CYTOKINES

Cytokines released from the liver following IR injury

A multitude of cytokines are upregulated in response to liver IR injury. Bezinover *et al*[57] evaluated cytokine upregulation in response to the ischaemia and reperfusion phases of human liver IR injury in 11 extended criteria donor grafts and 6 standard criteria donor grafts for liver transplantation. They obtained samples from the portal vein (prior to reperfusion, thought to represent the ischaemic phase of IR injury), the hepatic veins (at the beginning and end of post implantation liver flush with recipient circulating blood, thought to represent the reperfusion phase of IR injury) and arterial samples (from recipient prior to reperfusion and at 10 min and 20 min post reperfusion). Samples were analysed for TNF, IL-1, IL-2, IL-6 and IL-8 with comparison between levels of individual cytokines at each location. The results suggest early hepatic release of IL-6 during the ischaemic phase. This is followed by TNFα release (without observed increase in systemic circulating TNFα). IL-2 was likewise released from the liver towards the end of reperfusion. IL-1 was released from the liver during the process of reperfusion, without elevated levels seen in systemic samples. IL-8 and TNF are both known to be released by various cells including activated Kupffer cells in response to IR injury[58,59]. IL-8 is chemotactic, leading to recruitment of neutrophils to injured tissues[59], whilst TNFα is important for cell signalling leading to apoptosis or necrosis and neutrophil recruitment[60]. Interestingly, no difference was noted in IL-8 and TNFα release from standard and extended criteria groups. This is significant; given that extended criteria grafts are strongly associated with IR injury[21], higher concentrations of IL-8 and TNFα would be expected from this cohort. Thus release of IL-8 and TNFα may be associated with, but potentially not mechanistic to, IR injury and AKI development.

To summarise, in contrast to most published studies which focus on animal models, Bezinover *et al*[57] attempted to provide real-time human data on liver IR injury and hinted at possible temporal relationships between different cytokines in this context including IL-6, TNFα, IL-2 and IL-1. However, the study made significant assumptions, with no independent experimental validation of their methodology which matched sampling from different liver sites to the various phases of IR injury (for example portal vein sampling was matched to pre-reperfusion phase of injury). Such assumptions may explain the lack of expected difference in cytokine levels

between standard and extended criteria grafts. Additionally, the short period of reperfusion may explain the lack of correlation between liver flush samples and systemic samples. The "reperfusion phase" was only 20 min and therefore further changes within the liver during reperfusion injury may well have been missed in this data. Data from systemic blood samples over a longer time phase would have been interesting in this context.

A pilot study evaluating pre-conditioning in human liver transplantation performed in our unit investigated circulating cytokines at two hours post reperfusion. Levels of IL-6, IL-8, IL-10 and IL-17α were all significantly elevated, whilst plasma levels of IL-2, IFNγ and TNFα did not change during the peri-transplant period[61]. In addition, IL-10 was particularly associated with marginal grafts in this study, although small patient numbers mean that these data are not conclusive.

In a mouse model of 90 min partial hepatic IR injury (right lobe spared), Lee *et al*[62] demonstrated elevated serum IL-6, TNFα and MCP-1 at 6 h. These findings tallied with those from a previous study by the same authors that identified hepatic mRNA upregulation of TNFα, Intracellular Adhesion Molecule 1 (ICAM-1), Keratinocyte-derived Chemokine (KC), Monocyte Chemoattractant protein-1 (MCP-1) and Macrophage Inflammatory Protein-2 (MIP-2) following 60 min partial liver ischaemia [22]. This pattern of upregulation and protein expression is supported by other animal studies of hepatic IR injury[26].

In summary, investigation of liver cytokine release following IR injury has identified numerous molecules that may be present in serum and are capable of transmitting injury to the kidney. However, results between studies are conflicting and there is no clear evidence that the cytokines are responsible for AKI in this context. Further clinical studies that make use of targeted cytokine inhibition or specific rodent knockout models are required to link individual cytokines with AKI. Clarifying liver origin of the cytokine would also be important in establishing the pathway of injury. Additionally, single cell analysis of key liver cells in response to injury might help to identify new mediators of injury that have not been investigated to date.

Cytokines are primarily released from non-parenchymal cells in early liver IR injury

Non parenchymal cells (*i.e.*, non-hepatocytes) seem to be key in the mediation of early liver IR injury[63]. Sinusoidal endothelial cells are damaged during ischaemia, whilst Kupffer cells appear to be activated in response to reperfusion injury, demonstrating five times the TNFα production of control animals[64] in addition to IL-1 and superoxide anions[63]. TNFα production in Kupffer cells may be primarily driven by ROS[65]. In a rat model of liver transplantation, ischaemia-reperfusion preconditioned livers demonstrated a reduction in Kupffer cell superoxide formation, reduced TNF production and reduced non-parenchymal cell death leading to improved recipient survival[66], again suggesting that Kupffer cells are key in the mediation of injury. Acute liver graft failure has been linked to loss of viability of sinusoidal cells and activation of Kupffer cells, further demonstrating the importance of these cell types in the mediation of IR injury[64].

The late phase of liver reperfusion injury is categorised by infiltration of neutrophils, T lymphocytes and monocytes[67-69]. These cells are recruited to the liver parenchyma by upregulation of ICAM-1, VCAM-1 and MCP-1 on damaged hepatocytes and SECs. The infiltrating cells secrete matrix metalloproteinases, other proteases and ROS which cause further liver damage[68,70].

In summary, activation of non-parenchymal cells in the liver is fundamental for the early stages of IR injury. Inflammatory cells are recruited to the liver parenchyma by damaged hepatocytes and SECs and drive ongoing inflammation. Single cell analysis of non-parenchymal cells following liver IR injury may identify key transmitters of renal injury and clarify existing data.

The key cytokine culprits implicated in the mediation of renal injury

Many cytokines have been proposed as mediators of kidney injury following hepatic IR injury. Pulitano *et al*[71] performed molecular profiling of liver biopsies in 65 patients undergoing full size liver graft transplantation. Wedge biopsies were taken from the liver following graft preservation and 90 min after reperfusion in addition to serum samples preoperatively, 30 min after liver reperfusion and on post-operative days 1, 2, 5 and 7. 32% of recipients developed AKI. The authors demonstrated mRNA upregulation in 23 vasoactive, inflammatory, adhesion molecule, apoptosis inducing and oxidation genes (including ET-1, TNFα, IL-6, IL-18 and ICAM-1). Upregulation of the gene was correlated with serum expression of the protein for ET-1, TNFα, IL-6, IL-18 and RANTES 30 min post liver reperfusion and on post-operative days 1, 2, 5 and 7. Of the studied cytokines, only serum levels of Endothelin-1 (ET-1) and IL-18 were

independently associated with AKI development at post-operative day 1, suggesting a key role for ET-1 and IL-18 in the mediation of injury. Interestingly serum ET-1 also correlated with use of inotropes in donors and hepatic steatosis, both risk factors for liver IR injury, and so alternatively, ET-1 may be a surrogate marker for renal injury (which is related to severity of liver IR injury). Renal biopsies to evaluate local gene expression were not performed in this study and so the relationship between gene induction in the liver and effector genes for injury in the kidney cannot be established. Additionally, this study provides a limited look at 23 known mediators of inflammatory injury. Single cell analysis in this context would provide a more precise look at gene upregulation and potentially provide new targets for investigation.

At best, Pulitano *et al*[71] provides evidence for associations between liver mRNA upregulation, circulating IL-18 and ET-1 and kidney injury. However, causality is not established by these data and alternative explanations exist for the findings.

IL-18 may potentiate renal injury following liver IR injury with IL-18BP providing a protective effect

The IL-18-precursor is constitutively present in nearly all cells, where its activity is balanced by the high affinity IL-18 binding protein (IL-18BP). In its active form IL-18 is mostly secreted by macrophages, including Kupffer cells, although some disease processes lead to an imbalance of IL-18/IL-18BP with the liberation of free IL18 from other cell types. IL-18 is known to be an inducer of inflammatory cytokines[72]. Gonul *et al*[33] investigated the role of IL18 in renal injury post liver IR injury using a rat model of hepatic IR (clamping of portal triad for 1 hour followed by 4 h reperfusion) with administration of intraperitoneal IL-18BP 30 min before commencing the laparotomy for liver IR injury. There was no difference in liver IR injury (as measured by AST/ALT/LDH and histological damage) between the groups, but an almost 50% reduction in serum creatinine with administration of IL-18BP compared to controls. This was confirmed by a significant improvement in histological renal injury with a reduction in mononuclear cell infiltration, glomerular necrosis and tubular epithelial necrosis suggesting that IL-18BP does not modify the primary liver IR injury but is involved in the pathway for secondary renal injury. Findings in this study contrasted to a previous study by the same authors which demonstrated improvement in both liver-IR and renal injury with peritoneal administration of IL-18BP[72]. The authors attribute this difference to the higher dose of IL-18BP used in the first study (100μg versus 50μg in this study). This explanation is in keeping with an overall hypothesis of high IL-18 release in response to liver injury and subsequent haematological washout impacting secondary organs. Of note, both studies used human IL-18BP, which has limited homology with rat IL-18BP. This represents a fundamental flaw, and the studies would be better repeated with rat IL-18BP.

Overall IL-18 may be critical in the mediation of renal injury following liver IR injury. However, these data require validation with rat IL-18BP in the animal model, and successful translation of findings to the human setting.

ET-1 may contribute to renal injury post liver IR injury

In addition to the evidence regarding ET-1 provided above, circulating ET-1 has been demonstrated to correlate with both early reduction in GFR and long-term renal dysfunction in patients with normal renal function who are undergoing first Orthotopic Liver Transplantation (OLT)[74]. Patients with liver disease have background high circulating ET-1, due to increased synthesis and reduced clearance [75]. ET-1 is also significantly elevated at the end of the anhepatic phase of liver transplantation in clinical studies[76], although it may be cleared within 30 min by a functioning liver graft. The significance of this is unclear. ET-1 may contribute to renal injury or be a surrogate marker for MELD score and severity of liver disease, which is independently associated with worse outcomes post liver transplantation[77].

ET-1 has been demonstrated to promote Na^+ retention and increase renal vascular resistance without a significant change in blood pressure in healthy volunteers[78]. This function of ET-1 appears contradictory to evidence presented earlier where a reduction in renal resistive index was seen with reperfusion[24] and may reflect differences between the rat model and human situation or differences between the healthy liver and background liver disease or a compensatory mechanism in response to chronically high ET-1. Additionally, evidence suggests that the oxidative status of the renal microvasculature can significantly influence renal microcirculatory responses to ET-1 which may account for different results in different experimental settings. The vasoactive functions of ET-1 in the kidney may be mediated by its action to increase superoxide accumulation in preglomerular smooth muscle cells. Apocynin (an

NADPH oxidase inhibitor) has been demonstrated to attenuate ET-1's ability to reduce renal blood flow[79].

Cytokines recruit inflammatory cells to the kidney with potentiation of injury

In addition to the role they play in the mediation of liver IR injury, IL-6 and TNFα are upregulated in the kidney in response to liver IR injury. TNFα triggers leukocyte-endothelium interactions and microcirculatory dysfunction and is known to impact renal microvascular oxygen distribution and promote organ damage[27]. It has also been demonstrated to promote migration of inflammatory cells into the renal parenchyma through upregulation of KC (rodent equivalent of IL-8), MCP-1 and MIP-2, with macrophage recruitment[25,33]. This is similar to the functions of TNFα seen in the liver following IR as in section "*Cytokines released from the liver following IR injury*".

Likewise, IL-6 is a major pro-inflammatory cytokine that stimulates release of neutrophils from bone marrow, prevents neutrophil apoptosis and activates neutrophils to produce toxic enzymes. Additionally, IL-6 activates endothelial cells to express adhesion molecules and produce chemokines[43] which promote the recruitment of inflammatory cells to the renal parenchyma. Activated neutrophils release oxygen free radicals, neutrophil elastase and products of arachidonic acid metabolism, further potentiating renal injury[25,80].

Thus both IL-6 and TNFα are believed to be key for the potentiation of renal injury following liver IR injury by recruitment of inflammatory cells as part of the systemic inflammatory response to injury. Further investigation is required to establish other potentiators of injury in this context.

POTENTIATION OF INJURY WITHIN THE KIDNEY: THERE IS CELL TO CELL SIGNALLING OF DAMAGE

There is growing evidence for transmission of injury between cells in a variety of settings. Connexins are a big family of transmembrane proteins, expressed in all human organs and tissues, which form internal gap junctions between cells and manipulate small molecule (less than 1KDa), direct-transfer signalling[36]. Luo specifically investigated the role of Connexin-32 (Cx32), because this connexin is normally richly expressed in the kidney. Cx32 expression was found to increase following reperfusion in a rat model of liver transplantation, peaking in tandem with kidney damage and functional impairment at 8 h[36]. Treatment with 2-APB, a relatively specific inhibitor of Cx32 channels, reduced renal injury. This study only evaluated renal function and would have benefited from measurement of liver injury, both in response to IR and following addition of 2-ARB, to evaluate the specificity of the renal response.

Cx32 expression has been demonstrated to positively correlate to the degree of IR injury in liver biopsies from patients undergoing liver transplantation[81], but human evidence to support the role of Cx32 in subsequent kidney cell to cell transmission of injury is lacking. Such data is worth pursuing, along with supplementary evidence to further define cell to cell signalling in the kidney.

THE INJURED KIDNEY MAY MODULATE THE PROGRESSION OF LIVER IR INJURY

Accumulating evidence suggests that in addition to liver IR injury mediation of renal injury, the kidney itself plays a key role in the potentiation or amelioration of liver injury.

There is demonstrable liver injury after ischaemic renal injury, with derangement of AST/ALT and evidence of hepatocyte apoptosis (*via* activation of NFB-receptor)[82,83]. IL-10, IL-6 and TNFα are upregulated within the liver and multiple markers of oxidative stress have been identified following ischaemic AKI. It is not known whether this is related to systemic inflammation or targeted liver injury. Either way, the effect may be persistent; renal IR injury is associated with the development of hepatic steatosis in the longer term[80].

Human Heat Shock Protein 27 (HSP27) is a member of the chaperone protein family. These proteins are upregulated in response to a variety of cellular stresses. HSP27 is a key stabiliser of F-actin and a potent anti-apoptotic. In a genetically manipulated mouse model with demonstrated robust and widespread overexpression

of HSP27, Park *et al*[25] demonstrated attenuation of both partial liver IR injury (left and middle liver lobe inflow clamped), and secondary renal injury. The hepatic protection was primarily mediated by the kidneys as the liver injury was abolished by unilateral and bilateral nephrectomy. The findings of this study contrast with a previous study by the same group, where HSP27 overexpression provided primary protection against liver IR injury (significantly less necrosis and apoptosis at 2 h post reperfusion)[84]. In that study the HSP27 protection was thought to be mediated by Kupffer cells; depletion of Kupffer cells obliterated protection in HSP27 over-expressing mice but did not impact IR injury in wild type mice. Such results are not in keeping with the previously discussed, known roles of Kupffer cells in liver IR injury. One would expect obliteration of Kupffer cells in wild type mice to downregulate IR injury. Further investigation of these controversies is required but these studies hint that it might be possible to "switch off" liver IR injury and AKI, given the right therapeutic targets.

The sphingosine-1-phosphate (S1P)/$S1P_1$-receptor interaction on endothelial cells is known to be critical in the maintenance of endothelial barrier integrity in the kidney. In a mouse model of hepatic IR injury, pre-treatment with S1P did not significantly attenuate liver injury (ALT/histology) at 6 h but provided marked attenuation at 24 h [62]. Renal injury was reduced at 6 h (TUNEL assay), with significantly improved endothelial integrity and reduced expression of $CD44^+$ cells (indicating a reduction in endothelial injury) compared to non S1P treated mice. Pre-treatment with the $S1P_1$ antagonist, VPC 23019, partially reversed the protection afforded by S1P.

Together these studies support the hypothesis that renal injury is both triggered by early liver IR injury and modulates ongoing liver IR injury. The mechanisms by which this occurs remain unknown but may involve the systemic inflammatory response to renal injury. Further work is required to determine the "switches" that decide whether renal modulation is pro- or anti-inflammatory and to harness these for therapeutic intervention.

THERE MAY BE ADDITIONAL EXTRA-RENAL MODIFICATION OF LIVER IR AND RENAL INJURY

Some recent studies have focussed on the role of the intestinal immune system in primary renal injury leading to secondary liver injury. IL-17A released by Paneth cell degranulation in the small intestine in response to primary renal IR injury contributes to hepatic, renal and intestinal injury, with improvement in all three when IL-17A is depleted[85]. Contrastingly Paneth cell TLR-9 knockout mice demonstrate progression of hepatic, intestinal and renal injury in response to kidney IR injury[86]. These data are obtained from models of kidney IR injury and therefore do not directly relate to liver IR injury. However, future studies to investigate the role of Paneth cells in the mediation of renal and liver injury following IR insult to the liver may reveal similar intriguing findings and provide additional opportunities to modulate the potentiation of systemic and local response to injury.

LIMITATIONS OF THE CURRENT LITERATURE

The studies discussed within this review present some interesting data related to the mechanisms of renal injury secondary to liver IR injury. However, a clear understanding of the pathways mediating the transmission of injury from liver to kidney and back again is not yet within our grasp. Investigative work in this field has relied heavily upon small rodent models. Rodent models often lack applicability to the human setting and clinical interventions that show promise in rodents often fail upon translation to the human setting[44,61,87]. Rodent populations used for experimental work are inbred animals with relatively limited genetic diversity and so cannot fully represent human populations with polymorphic genetic backgrounds[88]. Liver injury often occurs in patients who do not have background "normal" liver (including transplantation, ALF and ACLF). Background altered liver function may prime the immune and/or renal systems to injury, potentiating the effects of an acute insult. This is not accounted for in rodent models and may also impact the applicability of any results to the human setting.

A second limitation with all studies in this field is the difficulty associated with defining AKI clinically. Most studies included here rely upon serum creatinine (+/-

urea), with clinical studies applying the AKIN or KDIGO criteria. Both AKIN and KDIGO rely upon changes in serum creatinine or urine output. Serum creatinine is well known to be a relatively insensitive marker of renal injury. Patients with end-stage liver disease are often deplete in skeletal muscle and so have low circulating creatinine, which may mask underlying renal injury[89,90]. Changes in serum creatinine take time to reflect renal injury, often between 12 and 24 h. During this time, renal injury may be potentiated, with worse long-term outcomes.

A third limitation with studies in this field is the lack of an animal model that allows serial sampling to dynamically assess changes over time. Rodent models are too small to accommodate serial liver and kidney biopsies or blood samples. As demonstrated herein, renal injury and liver injury following liver IR is a dynamic and evolving process. Serial, *in vivo* sampling would be highly informative.

FUTURE DIRECTIONS

Whilst the limitations of rodent models may be here to stay, improved diagnostic methodology for acute kidney injury may be provided by one, or a combination of biomarkers. NGAL shows great promise in this respect[91], and is already being used as an alternative to serum creatinine for the diagnosis of renal injury in some studies. In a study of liver transplant patients, we found that urinary NGAL measured at the time of abdominal closure accurately predicted post-operative AKI[23]. This has been confirmed by other studies[92,93]. The site of release and role of NGAL in liver IR injury leading to renal injury is not currently known. NGAL has multiple functions[94] including iron transport[95]. Speculatively, NGAL could "mop up" iron free radicals which contribute to injury in the context of liver IR and resultant renal injury. An interesting recent study identified that NGAL is co-localised with Arl13b to the primary cilium of human renal tubular epithelial cells in chronic allograft nephropathy [96]. KIM-1, another potential biomarker for renal injury[97] is also expressed on primary cilia[98]. The primary cilium is a key organelle and performs a variety of functions including mechano- and chemo-sensitisation[99]. In liver IR injury, primary cilia are shed into the urine and are demonstrable as early as 1 h post injury[98]. Whether NGAL is co-incidentally shed with cilia, or promotes shedding of cilia, awaits clarification.

CONCLUSION

The mechanisms by which liver injury mediates renal injury require further clarification but it is likely that multiple circulating molecules are involved, including currently unidentified molecules. The kidney may be primed to injury by alterations in renal microcirculation with early endothelial and subsequent tubular injury. Renal injury in turn, may potentiate liver IR injury and this process may involve other organs with immune function, including the gut.

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ORIGINAL ARTICLE

Retrospective Study

Unilateral hypoplastic kidney in adults: An experience of a tertiary-level urology center

Rabea Ahmed Gadelkareem, Nasreldin Mohammed

ORCID number: Rabea Ahmed Gadelkareem 0000-0003-4403-2859; Nasreldin Mohammed 0000-0002-0232-9497.

Author contributions: Gadelkareem RA designed the research, searched and collected the data, and wrote the paper; Mohammed N contributed to study design and manuscript writing and revision, and supervised the work; both authors approved the paper.

Institutional review board statement: This study was approved on November 25, 2021 by the Medical Ethics Committee of the Faculty of Medicine, Assiut University, Egypt as a topic in a research project titled "Experience of a tertiary-level urology center in the clinical urological events of rare and very rare incidence: a retrospective research project." The institutional review board number is 17300684.

Informed consent statement: This article is a retrospective one with only descriptive anonymous data. Patients were not required to give informed consent to the study because the manipulated data were anonymous and were obtained after each patient agreed to treatment by consent.

Conflict-of-interest statement: The

Rabea Ahmed Gadelkareem, Nasreldin Mohammed, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Assiut 71515, Egypt

Corresponding author: Rabea Ahmed Gadelkareem, MD, Associate Professor, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Elgamaa Street, Assiut 71515, Egypt. dr.rabeagad@yahoo.com

Abstract

BACKGROUND

Unilateral small-sized kidney is a radiological term referring to both the congenital and acquired causes of reduced kidney volume. However, the hypoplastic kidney may have peculiar clinical and radiological characterizations.

AIM

To evaluate the clinical presentations, complications, and management approaches of the radiologically diagnosed unilateral hypoplastic kidney.

METHODS

A retrospective review of the records of patients with a radiological diagnosis of unilateral hypoplastic kidney between July 2015 and June 2020 was done at Assiut Urology and Nephrology Hospital, Assiut University, Egypt.

RESULTS

A total of 33 cases were diagnosed to have unilateral hypoplastic kidney with a mean (range) age of 39.5 ± 11.2 (19-73) years. The main clinical presentation was loin pain (51.5%), stone passer (9.1%), anuria (12.1%), accidental discovery (15.2%), or manifestations of urinary tract infections (12.1%). Computed tomography was the most useful tool for radiological diagnosis. However, radioisotope scanning could be requested for verification of surgical interventions and nephrectomy decisions. Urolithiasis occurred in 23 (69.7%) cases and pyuria was detected in 22 (66.7%) cases where the infection was documented by culture and sensitivity test in 19 cases. While the non-complicated cases were managed by assurance only (12.1%), nephrectomy (15.2%) was performed for persistent complications. However, symptomatic (27.3%) and endoscopic (45.6%) approaches were used for the management of correctable complications.

CONCLUSION

Unilateral hypoplastic kidney in adults has various complications that range from

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urinary tract infections to death from septicemia. Diagnosis is mainly radiological and management is usually conservative or minimally invasive.

Key Words: Congenital anomalies; Hypoplastic kidney; Kidney size; Small sized kidney; Solitary kidney; Urolithiasis

Core Tip: The study reviewed the clinical characteristics, complications, and management of the unilateral hypoplastic kidney in adults. The various clinical presentations are due to the different complications including urolithiasis, obstruction, urinary tract infections (UTIs), and life-threatening morbidities such as anuria and septicemia. Renal radioisotope scanning is indicated for cases with sizable kidneys, verification of the decision of surgical intervention, and patient preference. Conservative and endoscopic approaches should be tried first for the management of complications. However, laparoscopic nephrectomy is recommended for the treatment of persistent complications such as hypertension and recurrent UTIs or urolithiasis.

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INTRODUCTION

The term "small-sized kidney" is an imaging-based description that defines the reduction of the kidney mass or volume[1]. It could be unilateral or bilateral, where the latter form is associated with the progression of chronic kidney disease through its different stages[2,3]. However, the unilateral small-sized kidney usually presents clinically with normal total renal functions due to the normal and, in many instances, compensating contralateral kidney[4,5]. It results from many contributing pathological entities such as congenital hypoplasia, chronic pyelonephritis, renovascular ischemia, and urological interventions and surgeries[6]. The hypoplastic kidney is a main contributing factor for this entity and is predominantly unilateral with acquired contralateral compensatory hypertrophy. Although the secreted urine in these kidneys may have normal constituents, its amount is low with subsequent urinary stasis. So, the hypoplastic kidney predisposes to urinary tract infections (UTIs) and urolithiasis. Its share in the total renal function is, definitely, lower than the other kidney down to warrant surgical removal, when indicated, without significant effect on the patient's total renal function. Hypoplastic dysplastic kidney could be confused with the chronic pyelonephritic kidney which results from repeated attacks of ascending infections. However, the etiology of the hypoplastic kidney is mostly attributed to developmental arrest due to ischemia during embryogenesis[7,8]. Our aim was to study the clinical presentations, radiological differences between the congenital and acquired causes, indications and lines of surgical intervention, and patient's perception of treatment.

MATERIALS AND METHODS

Study design

A retrospective search of the manual and electronic patients' records in our hospital was done for the patients who had a diagnosis of unilateral congenital small-sized kidney or hypoplasia between July 2015 and June 2020. Demographic variables including age and gender were studied. Also, clinical variables including the clinical presentations, laboratory and imaging investigations, complications, and management were studied. Patients' perception of the diagnosis that they had low function kidneys was traced in the records of their counseling and subsequent follow-up compliance according to the decision of management.

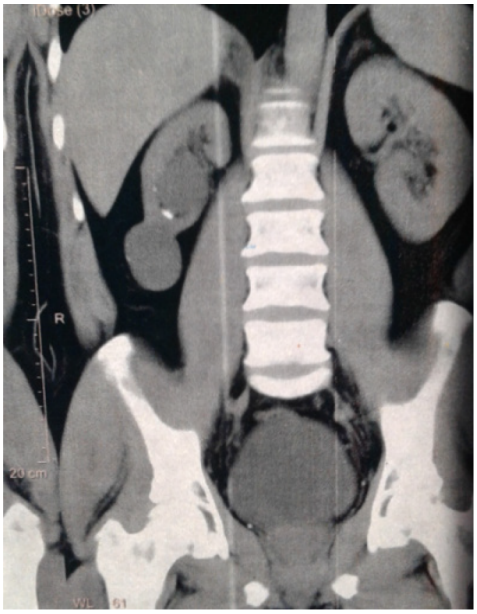

Figure 1 A 44-year-old male patient presented with right loin pain due to right hypoplastic kidney. A coronal view of non-contrast multi-slice computed tomography of the abdomen and pelvis showing the small-sized right kidney with a smooth outline, two simple cysts at the middle and lower poles, and a very small stone in the lower calyx. This case was managed conservatively.

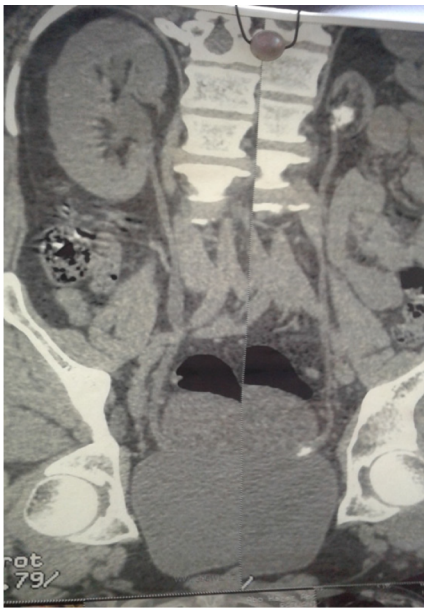

Figure 2 A 43-year-old male patient presented with irritative lower urinary tract symptoms due to a left hypoplastic kidney complicated by stones. A coronal view of non-contrast multi-slice computed tomography of the abdomen and pelvis showing the severely diminutive left kidney with non-obstructing stones in the renal pelvis and left intramural ureter. This case was managed by left ureteroscopy and nephrectomy.

Owing to the difficult differentiation between the hypoplastic kidney and atrophic causes of the unilateral small-sized kidney which could be accurately done only by histopathological studying, we employed the radiological features for the definition of the hypoplastic kidney as a kidney with smooth outline contour without strands in the surrounding fat (Figure 1), a length less than 9 cm or 3-vertebra height, or a glomerular filtration rate less than 40% of a total function that is not less than 60 mL/min/1.73 m^2. Patients who had documented acquired causes for the unilateral small-sized kidney including a previous treatment of urolithiasis by surgeries or extracorporeal shock wave lithotripsy, evidence of previous normal kidney size, previous partial nephrectomy, and vesicoureteral reflux disease were excluded from the study.

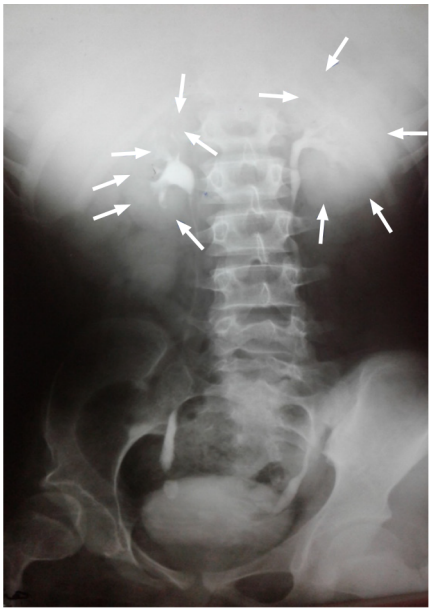

Figure 3 A 39-year-old female patient presented with right loin pain due to right hypoplastic kidney. An intravenous urography film showing the right hypoplastic kidney with preservation of the normal shape of the pelvicalyceal system and fine details of the whole kidney without obstruction, despite the presence of a right lower ureteral stone. Note the difference between the sizes of both kidneys that are outlined by the arrows.

Biostatistics

The data were descriptive and were presented as numbers and percentages or mean ± standard deviation. No biostatistician revision was warranted.

RESULTS

Thirty-three patients were included in the study. The demographic and clinical characteristics are summarized in Table 1.

Ultrasonography and plain radiography were routine imaging tools. However, computed tomography (CT) was the best tool for the characterization of the morphological features and complications (Table 2) (Figures 1 and 2). Intravenous urography was performed in two patient (Figure 3). Radioisotope scanning was performed for a limited number of cases (Table 3).

Urolithiasis was the most common complication of the hypoplastic kidney (Table 4). One patient died from septicemia due to obstructive pyelonephritis of the contralateral kidney after 2 years from the original diagnosis.

Different treatment approaches were used, including nephrectomy, endoscopic treatment of stones, conservative and symptomatic treatment, and assurance only for the cases without complications. Laparoscopic nephrectomy was performed in five cases for treatment of uncontrolled hypertension or persistent UTIs (Table 5).

All patients expressed concerns about the effect on the total kidney function. They had been educated that the lesion was unilateral and should not lead to end-stage renal disease. Four patients without complications preferred to have objective confirmation of the condition by renal radioisotope scanning including two potential kidney donors who were excluded from the donation (Table 3).

Follow-up duration varied between 7-56 mo. Three cases suffered from recurrent UTIs after stone removal and were managed conservatively.

DISCUSSION

The incidence of the small-sized kidney is variable in clinical settings[9]. Common causes of the unilateral small-sized kidney include chronic pyelonephritis, reflux or obstructive renal atrophy, and renovascular ischemia followed by the uncommon causes represented as congenital renal hypoplasia, tuberculosis, and partial nephrectomy[6]. The unilateral small-sized kidney which results from chronic pyelonephritis, congenital hypoplasia, or both represents a clinical difficulty[9].

Table 1 Demographic and clinical characteristics of the patients (*n* = 33), *n* (%)

Variable	Value
Age (yr)	
Mean ± SD	39.5 ± 11.2
Median (range)	40 (19-73)
Gender	
Male	19 (57.6)
Female	14 (42.4)
Main clinical presentations	
Ipsilateral loin pain	8 (24.2)
Contralateral loin pain	4 (12.1)
Bilateral or vague abdominal pain	5 (15.2)
UTI manifestations	4 (12.1)
Stone passer ± LUTS or colic	3 (9.1)
Anuria/oliguria	4 (12.1)
Accidental discovery F[1]	5 (15.2)
Anatomical side	
Right	23 (69.7)
Left	10 (30.3)
Laboratory investigations	
Serum creatinine mean ± SD; median (range) (mg/dL)	1.2 ± 0.68; 0.9 (0.66-3.6)
Positive for protein in urine	5 (15.2)
Patients with WBCs > 10/HPF in urine F[2]	22 (66.7)
Patients with RBCs > 3/HPF in urine	15 (45.5)

[1]F: Two cases of them were potential living donors and were excluded due to this anomaly and the other three cases were investigated for hypertension.
[2]F: In these cases, positive culture and sensitivity tests were reported in 19 cases (86.4%). HPF: High power field; LUTS: Lower urinary tract symptoms; RBCs: Red blood corpuscles; UTI: Urinary tract infection; WBCs: White blood cells.

Congenital anomalies of the urinary system are usually detected during childhood. However, when the lesion is commonly unilateral such as the hypoplastic kidney, it can pass unnoticed until the accidental discovery or development of complications in adulthood[10]. The common clinical presentations are related to the underlying complications of the hypoplastic kidney such as urolithiasis, recurrent UTIs, and hypertension[6,8]. Other rare presentations include vaginal dribbling due to ectopic ureteral insertion in females[11]. In the current study, loin pain was a cardinal presentation that refers either to the high incidence of complications including urolithiasis, hydronephrosis, and UTIs or the compensatory effect of the contralateral kidney[4-6,8].

Imaging represents a fundamental role in the urological practice with prompt advances through the last decades. Kidney size is a significant predictor of its function. Also, it is a cardinal item in urinary imaging and evaluation of the total renal functions. Bilateral reduction of renal size is imperatively associated with chronic renal impairment, especially with glomerulonephritis and other systemic parenchymal medical disorders[2,3].

Kidney size or volume and length are significant indicators for its function and affecting diseases. Measurement of the size of the kidney according to the old imaging modalities was two-dimensional and expressed relative to the corresponding vertebral heights such as in the plain and excretory radiographs[12]. However, many imaging modalities have been evolved and used recently for the measurement of three-dimensional kidney size. Among these modalities, ultrasonography has been the most practically used one, because it is available, simple, non-invasive, and repeatable. The

Table 2 Number of patients and abnormal findings (other than small-sized kidney) per imaging tool, *n* (%)

Imaging modality	Number of patients who had this imaging	Abnormal findings	*n* (%)
US	33 (100)	Stones	19 (57.6)
		Cysts	3 (9.1)
		Hydronephrosis	7 (21.2)
KUB	33 (100)	Stones	18 (54.6)
IVU	2 (6.1)	Hydronephrosis	1 (3)
MSCT	27 (81.8)	Stones	23 (69.7)
		Cysts	3 (9.1)
		Hydronephrosis	8 (24.2)

IVU: Intravenous urography; KUB: Kidney-ureter-bladder radiography; MSCT: Multi-slice computed tomography; US: Ultrasonography.

Table 3 Total and split renal functions represented by the glomerular filtration rate in patients who were evaluated by renal isotope scanning (*n* = 8), *n* (%)

Case No.	Age (yr)	Gender	GFR (mL/min/1.73 m^2)			Indication for isotope scanning
			Total	Right	Left	
Case 1	25	Male	92.4	61.9 (67)	30.5 (33)	Kidney donation
Case 2	42	Female	83.2	53.4 (64.2)	29.8 (35.8)	Kidney donation
Case 3	47	Female	88.5	67.8 (76.6)	20.7 (23.4)	To verify decision
Case 4	45	Female	69.7	61.2 (87.8)	8.5 (12.2)	Patient request
Case 5	21	Female	86	16.8 (19.5)	69.2 (80.5)	Patient request
Case 6	37	Male	77.6	58.2 (75)	19.4 (25)	To verify decision
Case 7	28	Male	83.4	17.5 (21)	65.9 (79)	To verify decision
Case 8	26	Male	66.8	7.5 (11.2)	59.3 (88.8)	To verify decision

Table 4 Rates of complications that occurred in patients with unilateral hypoplastic kidney (*n* = 29/33), *n* (%)

Complication	Number of patients	Involvement/localization		
		Ipsilateral	Contralateral	Bilateral/systemic
Urolithiasis	23 (69.7)	12 (36.4)	3 (9.1)	8 (24.2)
Renal cysts	3 (9.1)	2 (6.1)	1 (3)	0 (0)
Hydronephrosis	8 (24.2)	3 (9.1)	4 (12.1)	1 (3)
Recurrent UTI	10 (30.3)	1 (3)	2 (6.1)	7 (21.2)
Hypertension	3 (9.1)	NA	NA	3 (9.1)
Septicemia	1 (3)	0 (0)	1 (3)	1 (3)

NA: Not applicable; UTI: Urinary tract infection.

length and size of the kidney correlate and are usually expressed relative to the whole body anthropometric measures. Size is more accurately expressed as volume by three dimensions which are length, width, and thickness with approximate mean values of 12 cm, 6 cm, and 3 cm, respectively. In spite of the absence of consensus about the definite normal values of renal dimensions among the different populations, renal length is a reproducible, accurate, and more valuable tool for studying renal diseases in adults[12-14]. Accordingly, and in parallel to these established findings, the imaging-based definition was considered in the current study. The need for

Table 5 Management approaches for patients with unilateral hypoplastic kidney (*n* = 33), *n* (%)

Approach of management	Category/variety	*n* (%)
Assurance only		4 (12.1)
Conservative/symptomatic treatment F[1]	Total number of patients who received the treatment F[1]	9 (27.3)
	For hypertension	2 (6.1)
	For UTI	3 (9.1)
	For stones	5 (15.2)
	Hydronephrosis	1 (3)
	For cysts	1 (3)
Shock wave lithotripsy		8 (24.2)
	Ipsilateral	2 (6.1)
	Contralateral	5 (15.2)
	Bilateral	1 (3)
Endoscopic procedures		
	Ipsilateral ureteroscopy	3 (9.1)
	Contralateral ureteroscopy	3 (9.1)
	Contralateral JJ placement	5 (15.2)
Laparoscopic nephrectomy		5 (15.2)
	For recurrent UTI	2 (6.1)
	For hypertension	3 (9.1)
Open nephrectomy		1 (3)
	For stones	1 (3)

[1]F: Many patients received conservative treatment for more than one element of complications, while others received it for certain complications and, at the same time, received surgical interventions for other complications. Also, some patients had failed conservative treatment before surgical interventions. JJ: Double-J ureteral stent; UTI: Urinary tract infection.

documentation of the reduction of renal function was warranted only in patients with a relatively minimal size reduction, verification of the interventional management including nephrectomy, and patient insistence on numerical documentation of function. Otherwise, the severe reduction in kidney size and signs of compensation of the contralateral kidney were enough to settle the management decision in most of the cases.

Radiographic features of the uncomplicated hypoplastic kidney include a smooth outer contour of the kidney with a reduced number of calyces without caliceal clubbing or dilatation. However, these features, especially the caliceal morphology, could be disturbed in complicated cases such as urolithiasis and UTIs. These changes may concern its morphological differentiation from the atrophied kidney due to chronic pyelonephritis with an irregular contour and clubbed or dilated calyces due to scarring of the parenchyma which exerts traction forces between the renal surface and the caliceal cavity[6,8]. Renal radioisotope scanning is a tool for accurate and numerical evaluation of renal function[15]. Also, the resistive index by Doppler ultrasound showed a favorable sensitivity in the differentiation of the atrophied and hypoplastic kidneys[16]. In the current study, the indicators of the acquired affection were used to exclude patients with those findings from the study.

In cases of uncomplicated congenital hypoplastic kidney, no symptoms or therapeutic interventions are warranted. However, the management of hypoplastic kidneys is usually directed to the complications rather than the anomaly itself[10]. Indications for nephrectomy include hypertension, recurrent infections, and urolithiasis. In our series, nephrectomy was mainly done for hypertension in relatively young patients, whatever was the degree of hypertension. In the old patients, nephrectomy was preserved for those patients who had uncontrolled hypertension or those who received multiple drugs of more than one antihypertensive drug group for

control. Stone passer and UTIs were other indications for surgical removal of the hypoplastic kidney.

Advantages of this series include its presentation in the time that the clinical studying of the clinical entity of hypoplastic kidney in adults has become scarce in the literature[10]. Also, it presented the classic clinical setting of the hypoplastic kidney with the patients' perception of the potential implications of the disease. Moreover, it provided the clinical experience of a high-volume center and a tertiary level urology hospital with wide geographical drainage of urological disorders. Retrospective studying may not allow an ideal design for studying. However, it is the most suitable form for rare conditions.

CONCLUSION

In conclusion, unilateral small-sized kidney in adults is a radiological diagnosis. The hypoplastic kidney is a contributing pathology with various clinical presentations due to the development of complications. Although routine imaging by abdominal ultrasonography and radiography is available, abdominal CT is commonly indicated due to complications. In the current study, renal radioisotope scanning was indicated for relatively sizable kidneys, verification of the decision of surgical intervention, and patient request for confirmation of the lesion. The unilateral small-sized kidney is commonly being complicated by urolithiasis, obstruction, or UTIs resulting in more aggressive and life-threatening morbidities such as anuria and septicemia. Endoscopic interventions are mainly for the management of urolithiasis. While conservative management is commonly planned for this lesion, interventional management approaches including nephrectomy are mainly performed for treatment of the complications such as hypertension and recurrent UTIs or urolithiasis.

ARTICLE HIGHLIGHTS

Research background

Unilateral small-sized kidney is a radiological term referring to both the congenital and acquired causes of reduced kidney volume. However, the hypoplastic kidney may have peculiar clinical and radiological characteristics. Its symptomatic clinical presentations are mostly attributed to the occurrence of underlying complications warranting early and proper management.

Research motivation

There is a noticeable lack of research on the clinical aspects of the unilateral hypoplastic kidney in the updated literature. Presentation of the current series may help enrich the literature and enhance the practice.

Research objectives

To study the clinical characteristics, complications, and management approaches of the unilateral radiologically diagnosed hypoplastic kidney in adults.

Research methods

A retrospective study was carried out on patients with a radiological diagnosis of unilateral hypoplastic kidney between July 2015 and June 2020 at a tertiary-level urology center in Egypt. The demographic, clinical, and radiological characteristics and management approaches were reviewed.

Research results

The study included 33 cases with unilateral hypoplastic kidney with a mean (range) age of 39.5 ± 11.2 (19-73) years. Loin pain (51.5%) was the main clinical presentation followed by the accidental discovery (15.2%), anuria (12.1%), manifestations of urinary tract infections (UTIs; 12.1%), and stone passer (9.1%). Radiological diagnosis was commonly done by CT showing the main features including the small volume and the preserved smooth outline and structures. Urolithiasis occurred in 23 (69.7%) cases and pyuria was detected in 22 (66.7%) cases where UTIs were documented by culture and sensitivity test in 19 cases. The non-complicated cases were managed by assurance only (12.1%), symptomatic (27.3%) and endoscopic (45.6%) approaches were used for

the management of simple and correctable complications, and nephrectomy (15.2%) was performed for persistent complications.

Research conclusions

There are various presentations for the unilateral hypoplastic kidney ranging from accidental discovery to UTIs that may lead to death by septicemia. The diagnosis is mainly radiological and management is usually conservative or minimally invasive relative to the underlying findings.

Research perspectives

Presentation of the clinical characteristics and outcomes may enhance the relevant urological practice of this disease. Urologists can provide the proper management including the conservative approaches for the simple complications and laparoscopic nephrectomy for the persistent complications.

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REVIEW

Hidden risks associated with conventional short intermittent hemodialysis: A call for action to mitigate cardiovascular risk and morbidity

Bernard Canaud, Jeroen P Kooman, Nicholas M Selby, Maarten Taal, Andreas Maierhofer, Pascal Kopperschmidt, Susan Francis, Allan Collins, Peter Kotanko

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Bernard Canaud, Allan Collins, Global Medical Office, Fresenius Medical Care, Bad Homburg 61352, Germany

Bernard Canaud, Department of Nephrology, Montpellier University, Montpellier 34000, France

Jeroen P Kooman, Department of Internal Medicine, Maastricht University, Maastricht 6229 HX, Netherlands

Nicholas M Selby, Maarten Taal, Centre for Kidney Research and Innovation, Academic Unit for Translational Medical Sciences, School of Medicine, University of Nottingham, Derby DE22 3DT, United Kingdom

Andreas Maierhofer, Pascal Kopperschmidt, Global Research Development, Fresenius Medical Care, Schweinfurt 97424, Germany

Susan Francis, Sir Peter Mansfield Imaging Centre, University of Nottingham, Nottingham NG7 2RD, United Kingdom

Peter Kotanko, Renal Research Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10065, United States

Corresponding author: Bernard Canaud, MD, PhD, Emeritus Professor, Global Medical Office, Fresenius Medical Care, 1 Else Kroner Str, DE-61352, Bad Homburg 61352, Germany.
bernard.canaud@fmc-ag.com

Abstract

The development of maintenance hemodialysis (HD) for end stage kidney disease patients is a success story that continues to save many lives. Nevertheless, intermittent renal replacement therapy is also a source of recurrent stress for patients. Conventional thrice weekly short HD is an imperfect treatment that only partially corrects uremic abnormalities, increases cardiovascular risk, and exacerbates disease burden. Altering cycles of fluid loading associated with cardiac stretching (interdialytic phase) and then fluid unloading (intradialytic phase) likely contribute to cardiac and vascular damage. This unphysiologic treatment profile combined with cyclic disturbances including osmotic and

electrolytic shifts may contribute to morbidity in dialysis patients and augment the health burden of treatment. As such, HD patients are exposed to multiple stressors including cardiocirculatory, inflammatory, biologic, hypoxemic, and nutritional. This cascade of events can be termed the dialysis stress storm and sickness syndrome. Mitigating cardiovascular risk and morbidity associated with conventional intermittent HD appears to be a priority for improving patient experience and reducing disease burden. In this in-depth review, we summarize the hidden effects of intermittent HD therapy, and call for action to improve delivered HD and develop treatment schedules that are better tolerated and associated with fewer adverse effects.

Key Words: End stage kidney disease; Cardiovascular mortality; Dialytic morbidity; Circulatory stress; Biologic storm; Dialysis sickness; Personalized medicine

Core Tip: In this in-depth review, we summarize the hidden effects of intermittent hemodialysis (HD) therapy, namely, dialysis sickness and dialysis related morbidity. We call for action to improve delivered HD and develop treatment schedules that are better tolerated and associated with fewer adverse effects. The final aim is to reduce cardiovascular burden and improve patient outcomes.

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INTRODUCTION

Conventional hemodialysis (HD) is a mature treatment that sustains life in almost 3 million patients with end stage kidney disease (ESKD) worldwide and provides a valuable bridging solution to kidney transplant[1-4]. However, by nature intermittent HD is an imperfect treatment that only partially corrects uremic abnormalities, increases cardiovascular risk, and is associated with a high disease burden[5-11]. The high treatment costs of renal replacement therapy represent in addition a significant health economic burden[12-14].

Recent evidence indicates that conventional high efficiency thrice-weekly intermittent HD schedules may be harmful to patients by provoking alternating cycles of fluid loading associated with cardiac stretching during the interdialytic period and fluid unloading that contribute to cardiac and vascular damage. This unphysiologic loading and unloading phenomenon combined with cyclical disturbances including osmotic and electrolytic shifts may contribute to dialytic morbidity and augment the health burden associated with the treatment of uremia[15-17].

Over past few years, several studies have emphasized the importance of ensuring optimal fluid volume and arterial pressure control, as well as adequately dosed and better tolerated dialysis therapy to improve patient outcomes[18]. The benefits of a dry weight first policy approach has been reinforced by interventional studies[19-21]. Fluid volume guidance has also been facilitated by means of supportive tools[22-24]. On the other hand, prospective clinical studies not only have documented that intermittent treatment might cause significant circulatory stress depending on treatment time and schedule[10,25-27], but have also shown that guided interdialytic and/or specific dialysis-based interventions might be able to reduce this risk[10,28,29].

However, few reports have focused on all aspects of dialysis patient management in a comprehensive way[30-32]. In this in-depth review, we summarize potential harmful effects of intermittent HD and propose solutions for achieving more cardioprotective and tolerable treatment.

INTERMITTENT EXTRACORPOREAL RENAL REPLACEMENT THERAPY IS THE SOURCE OF PERMANENT STRESS IN MAINTENANCE HD PATIENTS

Cardiocirculatory stress

The ‘unphysiology’ of intermittent HD is recognized as a leading cause of dialysis intolerance and multiorgan morbidity[33,34]. This phenomenon was exacerbated by operational changes that resulted in

shortening of dialysis treatment schedules and increasing dialysis efficiency[35]. As such, intermittent HD generates periodic changes in volume and blood pressure, osmotic shifts, and variation in circulating levels of compounds and electrolytes. Treatment-induced disturbances are in complete contrast with strictly regulated and stable conditions of the internal milieu in healthy subjects[32,36,37] (Figure 1).

During the interdialytic period, anuric HD patients tend to accumulate sodium and fluid according to fluid and diet intake, leading to chronic fluid overload[38]. In this condition, fluid overload has two components: The first, resulting from cyclic changes imposed by intermittent treatment marked by weight gain and progressive increase of systemic arterial pressure and pulmonary arterial pressure with cardiac stretching occurring between two treatment sessions; and the second, which reflects chronic fluid overload that has accumulated over time, exposing patients to chronic cardiac stretching and structural cardiac remodeling[39] (Figure 1).

During the intradialytic period, sodium and fluid removal resulting from ultrafiltration (intradialytic weight loss) and the patient to dialysate sodium gradient contributes to reducing circulating blood volume and triggering an adaptative hemodynamic response[40,41]. In response to ultrafiltration provoking a reduction in blood volume and cardiac stroke volume, arterial pressure and tissue perfusion are maintained by an increase in vascular tone, mainly through vasoconstriction of alpha-adrenoceptor territories, and an increase of vascular refilling and in venous return[42,43]. Recent intradialytic imaging studies have shown that reductions in myocardial perfusion and contractility (myocardial stunning) are linked to ultrafiltration rate that happens even without ischemic cardiac disease[17,44,45]. Several observational studies have reported a strong association between mortality and high ultrafiltration rate or volume changes, drop in blood pressure, and end-organ ischaemic insult [10]. The systemic response is more complex than a simple reaction to hypovolemia, since it incompasses others factors such as vascular refilling capacity, thermal balance, electrolyte fluxes, nutrient losses, as well as the individual patient's baseline cardiac reserve and neurohormonal stress responses[45,46]. Interesting, this response may be mitigated by various factors (*e.g.*, age, gender, comorbidity, and medication) explaining individual or temporal variations in hemodynamic response [38,47]. The hemodynamic stress induced by dialysis must be considered as a potent disease modifier in highly susceptible patients[48] (Figure 1).

Whatever the exact contribution of these phenomena, dialysis-induced cyclical volemic changes (hyper- and hypo-volemia) provoke alternating cardiac loading and unloading. This volemia variation cycle is responsible for repetitive myocardial stretching, a mechanism that leads to release of inflammatory mediators and promotes cardiac fibrosis and arrhythmias[49,50] (Figure 1).

Inflammatory stress

Bio-incompatibility (or more specifically, hemo-incompatibility) of the extracorporeal blood circuit and its systemic effects is a well identified issue associated with several aspects of dialysis related morbidity [51,52]. In brief, the activation of a cascade of serum proteins and blood cells is induced upon contact with foreign material in the extracorporeal circuit[53,54], and endothelial damage may further induce a vascular endothelial breach[55]. This process is further modified by the geometry, design (*e.g.*, blood air interface and dead space), and nature of blood tubing (*e.g.*, type of polymer and plasticizer) or dialyzer membrane (*e.g.*, cellulosic and synthetic), and may be amplified by microbial-derived products from dialysis fluid (*e.g.*, lipopolysaccharide, endotoxins, and bacterial DNA)[56-59]. As a result, endothelial cells and circulating blood cells (*e.g.*, platelets, leukocytes, and monocytes) are primed and activated to release pro-inflammatory mediators (*e.g.*, platelet activating factor 4, beta-thromboglobulin, granulocytes proteinases, anaphylatoxins, and cytokines) and activate protein cascades (*e.g.*, clotting cascades, complement activation, surface contact, and kallikrein-kinin system)[60-66]. Activation of the innate immune and coagulation systems amplifies and propagates this reaction[67]. Platelets and endothelial cell activation trigger coagulation, endothelial damage, vascular reactivity, and pulmonary trapping of cells. Mononuclear leukocyte activation results in the release of enzymes (*e.g.*, granulocyte neutral proteinase and elastase)[60,68-70], and increases their reactivity and adhesiveness that may cause obstruction at the microcirculatory level. In the lungs, this may contribute to hypoxemia[71-73]. Activation of monocytes and macrophages induces release of proinflammatory cytokines [interleukin (IL)-1, IL-6, and tumor necrosis factor-α][74,75]. In addition, acute inflammatory reactions are amplified by oxidative stress in an amplifying loops contributing to a vicious circle[74]. Seminal studies performed in various HD settings (*e.g.*, cellulosic *vs* synthetic dialyzers and contaminated *vs* ultrapure dialysate) have documented the importance of this "biologic storm" and provided evidence of its damaging effects (*e.g.*, allergic reaction, lung dysfunction, thrombocytopenia, and inflammation)[67,76] (Figure 1).

Despite significant improvements in extracorporeal circuit biocompatibility and wide-spread use of ultrapure dialysis fluid, systemic hemobiological reactions periodically induced by extracorporeal treatment[77,78] are likely to contribute to a micro-inflammatory state in chronic HD patients that amplifies long-term deleterious effects[30,75,79] (Figure 1).

Biological stress

In the absence of significant kidney function, internal metabolic processes and dietary intake produce metabolites during the interdialytic phase that steadily accumulate over 48 h and lead to classical

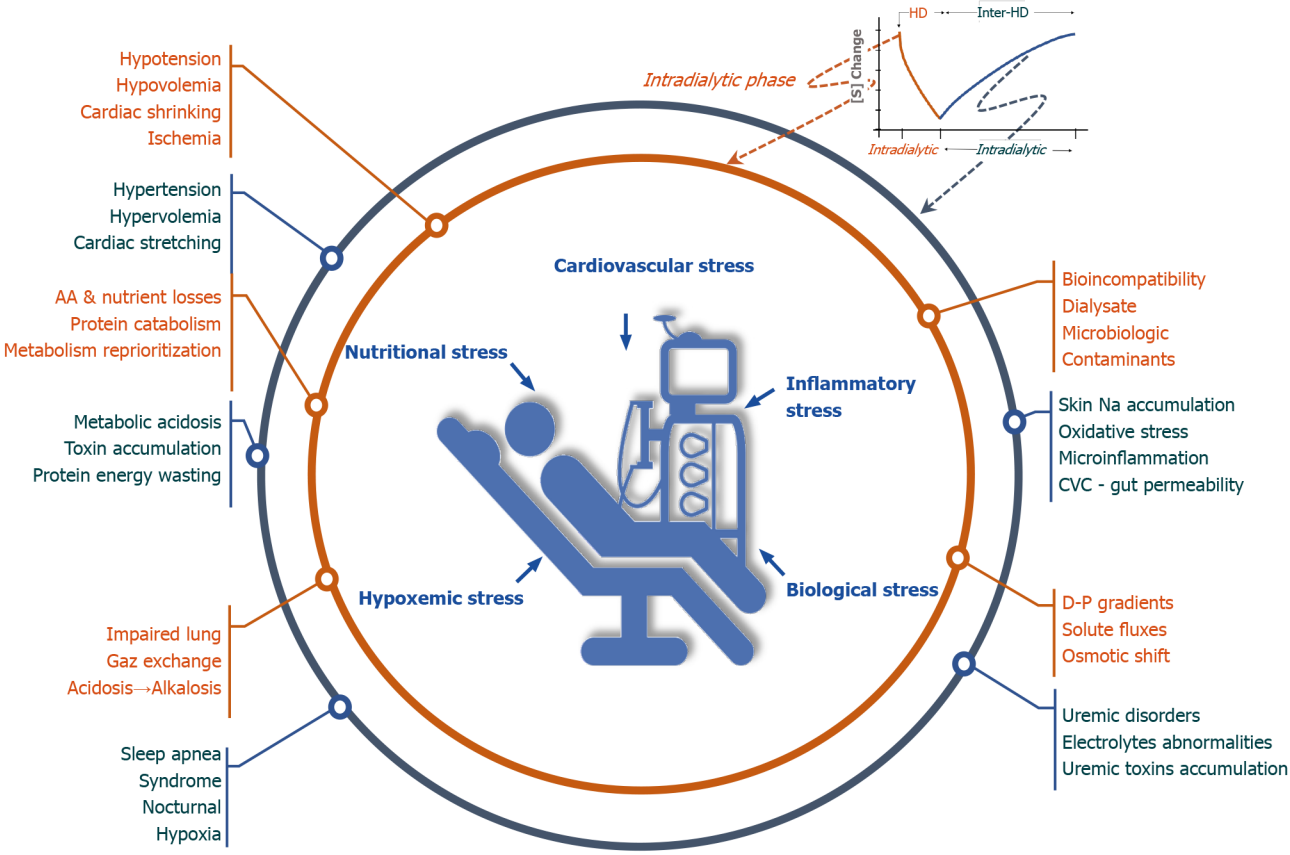

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Figure 1 Intermittent extracorporeal renal replacement therapy is the source of permanent stress in hemodialysis patients. HD: Hemodialysis; CVC: Central venous catheter.

biologic uremic abnormalities[80]. During dialysis, biologic disorders are usually corrected, at least partially, within 4 h. Biologic gradients between the dialysate and blood may be large, resulting in high amplitude changes of body composition during each session[32,76,81,82]. This gradient stress may be easily quantitated by dialysate-blood gradient concentrations and time averaged deviations for various solutes that are exchanged during the dialysis session[81]. Solutes exchange in HD follows negative or positive gradients, knowing that solute gradient is conventionally defined as dialysate-plasma concentration difference. Uremic retention toxins (*e.g.*, urea, creatinine, uric acid, potassium, and phosphate) are removed according to a negative gradient from blood to dialysate, while selected electrolytes (*e.g.*, bicarbonate, calcium, and magnesium) or nutritional compounds (*e.g.*, glucose) may move in the opposite direction. Unwanted removal of essential nutrients (*e.g.*, amino acids, peptides, and water soluble vitamins such vitamin D) and albumin may occur, contributing to a nutritional stress. The description of biochemical changes during dialysis is beyond the scope of this review. Through this remark we emphasize the fact that dialysis patients are challenged by various and large osmotic changes due to movements of urea and uraemic metabolites, water shift from extra- to intra-cellular space, acid-base changes moving the patient from metabolic acidosis to mixed alkalosis, potassium swings from hyper- to hypo-kalemia, and divalent ion alterations moving from hyper- to hypo-phosphatemia and from hypo- to hyper-calcemia, while at the same time patients are losing amino acids and other important nutrients[83-86]. Clinical manifestations of these metabolic derangements range from none, through minor to severe symptoms (fatigue, headache, and cognitive impairment), with the most extreme manifestation being dialysis disequilibrium syndrome[87,88] (Figure 1).

Hypoxemic stress

During dialysis, in addition to circulatory stress and impaired tissue perfusion[89-91], hypoxemia may occur, which can be particularly marked in the early phase of a dialysis session, likely related to hemoincompatibility reactions inducing leukocyte trapping within the lungs. This observation suggests the occurrence of an additional respiratory stress resulting from impaired pulmonary gas exchange[92, 93]. Prolonged intradialytic hypoxemia is likely to play an aggravating role in end organ damage by reducing further tissue oxygen delivery. We can speculate that this is a pathophysiologic link that explains the increased mortality observed in patients presenting with prolonged hypoxemia during HD [92] (Figure 1).

During the interdialytic phase, sleep apnea syndrome (SAS) and nocturnal hypoxemia have emerged as important additional cardiovascular risk factors in HD patients[80]. SAS marked by repetitive pause of breathing during sleep resulting in hypoxemia and hypercapnia is highly prevalent in HD patients [80,94]. In addition, SAS is associated with profound changes in cardiac loading conditions, lung arterial pressure, and autonomic activation, all factors that have been associated with significant cardiovascular morbidity such as left ventricular hypertrophy or arrhythmias and sudden cardiac death[95-98]. Although uremic abnormalities contribute to the development of SAS, the role of fluid overload exacerbating upper airways obstruction should not be neglected as recently pointed out by a study exploring fluid displacement into nuchal and peripharyngeal soft tissues in healthy subjects[99]. It is therefore tempting to speculate that chronic fluid overload is partly responsible for an edema of upper airway especially during sleep while in the supine position, thereby contributing to the occurrence of SAS (Figure 1).

In brief, whatever mechanisms are associated with impaired pulmonary gas exchange in HD patients, occurring either during intradialytic or interdialytic phases, prolonged periods of hypoxemia are likely to represent an additional stressor[34] (Figure 1).

Nutritional stress

Loss of muscle mass is common in HD patients and represents one of the most important predictors of mortality[100,101]. Sarcopenia is the main component of the protein-energy wasting syndrome that results from complex uremic abnormalities and the adverse effects of HD treatment[102-104] (Figure 1).

On one hand, acute studies assessing muscle and whole body protein turnover conducted in stable patients have consistently demonstrated an imbalance in protein synthesis and degradation during HD sessions[105-108]. It has been also shown that losses of amino acids during HD, ranging between 8 and 10 g per session, contributed significantly to the net protein catabolism[85,109-111]. Interestingly, this amino acid loss leads to reprioritization of protein metabolism during HD sessions. Amino acid loss during HD stimulates muscle and liver protein catabolism in order to preserve plasma and intra-cellular amino acid concentrations. Furthermore, amino acid utilization for protein synthesis either by the liver or muscle is impaired in HD patients, mainly through activation of cytokine pathways (IL-6) rather than because of amino acid depletion[112-114]. Remarkably, amino acid repletion by IV administration during HD tends to increase muscle protein synthesis but does not decrease muscle protein breakdown [115]. It is also interesting to note that dextrose depletion (when dextrose-free dialysate is used)[116] and other aspects of HD including type of membrane (cellulosic *vs* synthetic)[117,118] and dialysate microbiologic purity[119,120] may modulate this muscle protein catabolism phenomenon[121] (Figure 1).

On the other hand, long-term precise nutritional studies conducted in stable patients under strict metabolic conditions have shown that HD-induced imbalance in protein metabolism[122,123] might be compensated for by dietary protein and caloric supplements[124,125]. As shown, the net negative protein metabolic imbalance observed on dialysis days might be compensated for by increasing dietary protein and caloric intake (about 25%) during non-dialysis days, leading to a neutral protein and caloric balance on a weekly basis[124,126]. However, in practice, this can be hard to achieve.

In brief, intermittent HD treatment is associated with repetitive nutritional stress conditions due to reprioritization of protein metabolism within the muscle and liver (Figure 1).

Dialysis sickness and dialysis related morbidity

Dialysis sickness (DS) refers to the concept that inter-, peri-, and intra-dialytic morbidity resulting from the hemodynamic, inflammatory, biological, hypoxemic, and nutritional stresses discussed above, and can result in the long-term in end organ damage as summarized in Figure 2.

Dialysis-related morbidity (intra- and peri-dialytic symptomatology) has a negative impact on patients' perception and on their quality of life (QoL)[16,48,93,127,128]. This can be measured by scoring scales according to patient reported outcomes measures (PROM) or patient reported experience measures (PREM)[129-131]. Intra- and inter-dialytic symptoms that include hypotensive episodes, cramps, headache, fatigue, pruritus, and sleep disorders are the most frequently reported[132]. PROMs, PREMs, and most domains of health related QoL are significantly reduced in patients treated by conventional HD and tend to be improved by daily or extended treatment schedules[133-135]. Furthermore, dialysis symptom burden has been shown to be associated with increased mortality and hospitalization risks. Indeed, these clinical performance indicators are strongly recommended to assess dialysis adequacy and patient experience[129,136-139] (Figure 1).

End organ damage results from exposure to hemodynamic and pulmonary stressors leading to poor tissue perfusion and oxygen delivery, which are further aggravated by biological and cytokine "storms". Multifactorial and repetitive systemic stressors induced by intermittent HD treatment are likely to have harmful long-term effects on the function and structural modeling of vital organs (*e.g.*, cardiac stunning, leukoaraiosis, gut ischemia, and hepato-splanchnic changes). Some of these cardiovascular effects are enhanced by chronic low-grade inflammation acting on endothelial dysfunction and contributing to poor outcomes[10,28,140-142]. The combination of cardiocirculatory stress, hypovolemia, and electrolyte changes occurring during HD sessions creates pro-arrhythmogenic conditions that may contribute to clinically significant cardiac arrhythmias during the interdialytic phase[143-147]. Cardiac structural changes following myocardial stunning and remodeling in response

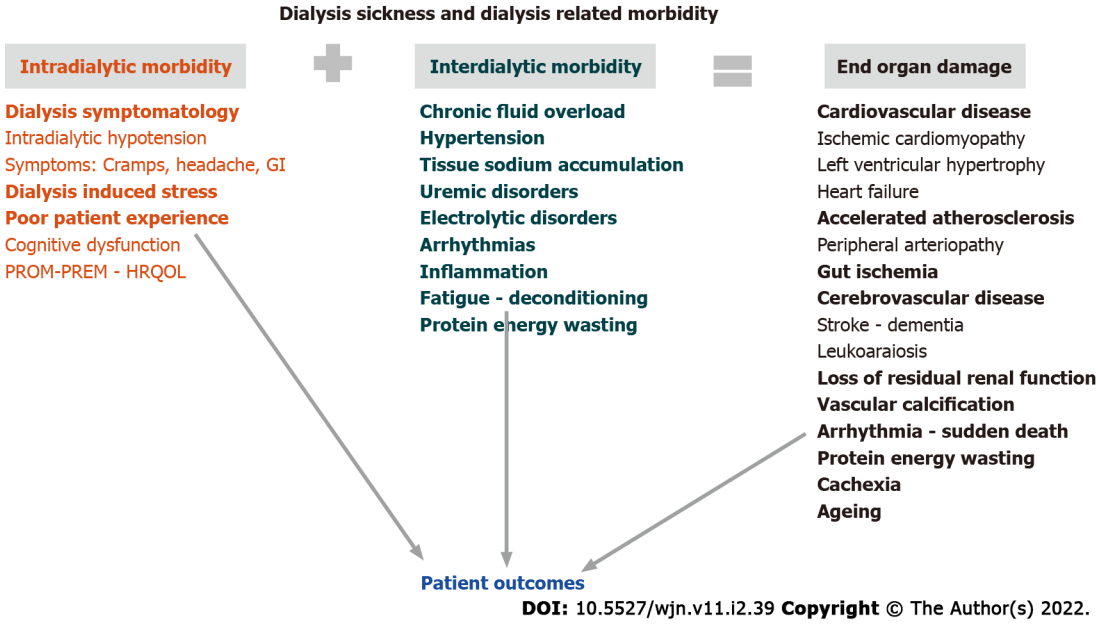


Figure 2 Dialysis Related Pathology linked to patient outcomes. GI: Glycaemic index; PROM: Patient reported outcomes measures; PREM: Patient reported experience measures; HRQOL: Health-related quality of life.

to cyclical dialysis-induced phenomenon, such as fibrotic scarring and loss of segmental contractile function with irregular electrical conductivity, are plausibly increasing the risk of sudden cardiac death [44,146,148-151]. These findings mimick the intense physiologic demands endured by healthy subjects under extreme conditions[152]. In order to mitigate dialysis-induced organ damage, we propose that conventional HD treatment schedule may be adapted and personalized, as a new treatment paradigm.

CALL FOR DESIGNING AND APPLYING A MORE CARDIOVASCULAR PROTECTIVE HD TREATMENT

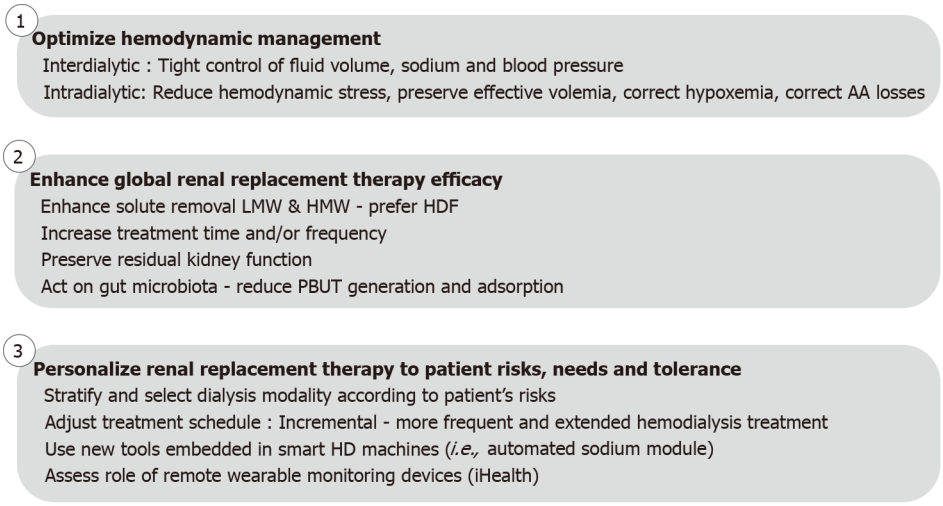
Optimizing hemodynamic management

The inevitable sodium and fluid accumulation that occurs during the interdialytic phase in anuric HD patients is responsible for chronic extracellular fluid overload with its adverse effects[153,154]. Hypertension is part of this constellation of disorders being recognized as the leading cause of cardiac and vascular disease in HD patients[19,20]. Management of fluid volume has been identified as a specific cardiovascular risk factor: On one hand, persistence of chronic fluid overload is independently associated with increased cardiovascular risk[155]; on the other hand, overly-rapid fluid volume reduction (*i.e.*, ultrafiltration rate) and hypovolemia are also associated with an increased risk of cardiovascular mortality[10,156] (Figure 3).

In other words, sodium and fluid volume homeostasis and blood pressure need to be managed more precisely during the interdialytic phase to achieve suitable targets. Additionally, hemodynamic stress secondary to volume contraction should be mitigated during dialysis by the use of appropriate tools and adjustment of the treatment schedule. Better monitoring of blood pressure and hemodynamics that are applicable to the clinical setting are also needed. This is a fundamental challenge of intermittent HD (Figure 3).

Improving sodium, fluid volume, and pressure management during the interdialytic phase: Salt and fluid management of the dialysis patient represents a major challenge for clinicians. A combined approach is needed that includes clinical management (a dry weight probing policy, *e.g.*, ultrafiltration, dialysate sodium prescription, and diet education) supported by assessment tools (*e.g.*, multifrequency bioimpedance and lung ultrasound)[157], cardiac biomarkers [*e.g.*, B-type natriuretic peptide (BNP) and NTproBNP], HD technical options (*e.g.*, sodium control module), and algorithms (*e.g.*, artificial intelligence) using advanced analytics in the future[38,158] (Figure 3).

Reducing hemodynamic stress induced by HD: Intradialytic morbidity (*i.e.*, fatigue, headache, cramps, hypotension, and alteration of cognitive function) is largely dependent on fluid removal (*i.e.*, ultrafiltration) and dialysis efficiency (*i.e.*, osmotic and solute concentration changes, and electrolytes shifts). The intensity and frequency of these symptoms also depend on patient characteristics (*e.g.*, age, gender, and anthropometrics), metabolism, and body composition, and on the HD treatment schedule



DOI: 10.5527/wjn.v11.i2.39

Figure 3 Action plan to design and implement a more cardioprotective renal replacement treatment in order to improve patient outcomes.
HD: Hemodialysis; PBUT: Protein bound uremic toxins; LMW: Low-molecular-weight; HMW: High-molecular-weight; HDF: On-line hemodiafiltration.

(*e.g.*, treatment time and frequency). It is well recognized that longer and more frequent dialysis treatment schedules are better tolerated with reduced circulatory stress and slower osmotic and electrolytic changes, as compared to short and less frequent dialysis schedules[159,160]. In that respect, ultrafiltration rate, reflecting fluid volume removed per time unit, is a well-recognized cardiac risk factor in dialysis patients that also associates with mortality risk[40]. In addition, it reflects the fact that biochemical gradients and solute fluxes are reduced per time unit, as well as osmotic changes and water shifts occurring within the central nervous system (Figure 3).

In a stepwise approach, increasing treatment time and/or dialysis frequency should ideally represent the first and most rational step to reduce risks associated with ultrafiltration rate and osmotic changes in non-compliant or fragile patients[161]. As a next step, modulating patients' hemodynamic responses through various tools embedded in the HD machine is another appealing option[162]. Monitoring blood volume during dialysis sessions is useful to identify critical volemia, to estimate remaining fluid in the interstitium, or to quantify vascular refilling capacity[163], but it is not sufficient to manage patient hemodynamic response[164]. Instead, surveillance of central venous oxygen saturation (ScvO2) in patients with central venous catheters may indicate critical changes in organ perfusion before they result in clinical symptomatology. Interestingly, the decline in $ScvO_2$ during dialysis has been correlated to ultrafiltration volume[165,166]. With arterio-venous fistula, near infrared spectroscopy, a non-invasive method, could be of interest to estimate tissue oxygenation[167]. Feedback controlled ultrafiltration system relying on blood volume changes has improved hemodynamic stability in selected studies, but so far has not improved patient outcomes and intradialytic morbidity[168,169]. Some studies have shown that using dialysate sodium and ultrafiltration profiling, with or without blood volume monitoring, may preserve intradialytic hemodynamic status but at the expense of an increased risk of subclinical salt loading, thirst, high interdialytic weight gain, and chronic fluid overload[170]. Adjusting dialysis thermal balance to preserve peripheral vascular resistance and cardiac output is also a simple strategy to improve hemodynamic tolerance that has been proven effective in several studies [171]. The main objective is to deliver isothermic or better, hypothermic dialysis, to prevent thermal gain during a dialysis session which is associated with an inappropriate hemodynamic response (vasodilation, tachycardia, and drop in ejection fraction)[172]. Hypothermic HD could be manually achieved by setting dialysate temperature 0.5-1 °C below the patient's core temperature. Automated thermal control of dialysis sessions requires the use of an online blood temperature monitor that can control precisely the thermal balance of patients to a preset target[173]. Both approaches reduce hypotension incidence (Figure 3).

Another important component of intradialytic morbidity relates to biochemical stress as reflected by the magnitude of dialysate-plasma solute gradient, a major determinant of solute fluxes[170,174-176]. Reducing instantaneous solute fluxes while keeping solute mass removal constant during dialysis session may be an interesting approach to reduce intradialytic morbidity. This issue could be easily addressed by reducing blood flow and increasing treatment time and/or frequency to slow instantaneous solute fluxes. This is a usual practice in Japan but it is not the most popular nor the most appealing in Western countries[177]. Another approach within the current short dialysis treatment schedule would be to continuously adjust flow parameters to reduce instantaneous solute fluxes while keeping solute mass transfer constant. Advanced technology will facilitate such an approach in the future, relying on microsensors positioned on dialysate side, feeding specific algorithms, and then

providing feedback control to the HD monitor to adjust relative flows and gradients (Figure 3).

In summary, one should consider that fluid volume removal and solute fluxes (dependent in part on blood-dialysate concentration gradients) are potentially modifiable factors of the dialysis prescription (Figure 3).

Enhancing renal care efficacy

The limited efficiency of contemporary HD in restoring the internal milieu composition and in controlling circulating levels of middle and large molecular sized uremic toxins, has stimulated use of convective-based therapies (*e.g.*, hemodiafiltration) and more porous membranes (*i.e.*, high cut-off)[36]. Therefore, the so-called 'residual syndrome', reflecting incomplete removal of uremic toxins, is another potential contributor to patient morbidity and mortality[178,179] (Figure 3).

Enhancing treatment efficiency by combining high efficiency hemodiafiltration and extended treatment time has been shown in recent studies to be able to address most remaining issues in adults. In brief, extended on-line hemodiafiltration (HDF) treatment has been associated with tight control of fluid volume and blood pressure without antihypertensive medications, normalization of phosphate levels while phosphate binders were stopped, correction of anemia while erythropoietic stimulating agent consumption was reduced by 50%, and a significant improvement of nutritional status and physical activity[180,181]. Interestingly, in a pediatric population, extended HDF has been also shown to improve intermediary outcomes (*i.e.*, fluid volume, blood pressure, inflammation, phosphate, and nutrition), to reduce cardiovascular disease progression, and to promote catch-up growth[182-184] (Figure 3).

Preserving residual kidney function is an important feature in dialysis patients since it is associated with a reduced disease and treatment burden and mortality[185-187]. Fluid volume and blood pressure control are usually better achieved with less dietary restriction[188]. Circulating levels of uremic toxins are significantly reduced, particularly for middle and large molecular weight substances but also for protein-bound uremic toxins[189]. In brief, all dialysis conditions, but particularly those ensuring a better hemodynamic stability, should be considered to prevent the repetitive ischemic kidney insults during HD[190] (Figure 3).

Acting on the gut to reduce protein-bound uremic toxin production has been recently suggested as a potential way of reducing circulating levels of protein bound uremic toxins (PBUT) such as indoxyl sulfate and paracresyl sulfate[191]. A few studies have confirmed positive effects of this option using either probiotics or adsorbers (AST120) administered orally in reducing plasma PBUT concentrations [192,193]. Unfortunately, published interventional studies have not confirmed potential long-term clinical benefits on patient outcomes[194] but further studies with better design and greater statistical power are warranted (Figure 3).

Personalizing renal replacement treatment schedule

Treatment schedule adaptation: A 'one–size–fits-all' approach is unlikely to work, and this should be kept in mind for optimizing renal replacement therapies in the future. Accordingly, dialysis prescription including treatment schedule (time and frequency), modality, dose, and efficiency[134,195,196], and electrolyte prescription should be tailored to patient profile, needs, and tolerance[197,198]. Furthermore, treatment prescription should be adapted over time to an individual patient's results in a personalized way to follow patient metabolic changes, treatment tolerance, and symptoms. Dialysis prescription should return to physiologic principles; it should not be the patient who must adapt to a fixed treatment, but the treatment should fit to the patient needs and tolerance instead.

In this context, the treatment schedules offered to patients should be expanded and become more flexible. It is not our intent to develop this concept further but to highlight recent interesting findings (Figure 3).

Incremental dialysis is an interesting concept that deserves more attention in particular in incident ESKD patients and in emerging countries[199]. It relies on the fact that HD acts as a complement to residual kidney function. In other words, the number of dialysis sessions and/or treatment time per week is inversely related to the glomerular filtration rate. Recent comprehensive reviews have addressed this issue to which we refer the interested reader for more details on clinical benefits and implementation[200]. In brief, incremental dialysis has the capacity to facilitate treatment implementation in new patients by reducing treatment burden, but also potentially to mitigate a shortage of renal replacement therapy resources in low and middle income countries (Figure 3).

Extended HD schedules (*i.e.*, long and nocturnal dialysis, alternate day dialysis, and daily HD) appear particularly attractive in terms of improving outcomes[181]. Extended treatment schedules must be viewed from two aspects: On one hand, outcomes are favorable including with kidney transplant [195,201-204]; on the other hand, they increase treatment burden and cost, except if home HD is chosen [205]. In this context, to solve both logisitical and cost issues, it is therefore proposed to develop extended treatment schedules at home or in self-care facilities[206] (Figure 3).

Use of new tools for monitoring and adapting treatment prescription: A whole body bioimpedance cardiography (BIC) non-invasive device has been assessed in HD patients. BIC has interesting features to measure the hemodynamic response to fluid removal (*e.g.*, cardiac output and total peripheral

vascular resistance) during dialysis. Based on these findings, it has been suggested that dialysis patients might be clustered into various categories defined as low or high cardiac output, low or high total peripheral vascular resistance, or normal hemodynamics[207,208]. BIC has the potential to support physicians to individualize dialysis treatment, although this would need to be tested in interventional studies[208]. Approaches using BIC warrant further studies to validate measurements and explore impact on patient outcomes[209] (Figure 3).

More recently, lung ultrasononography (LUS) has been proposed as a point-of-care tool to complete physical examination[24,210,211]. Lung ultrasound is a noninvasive method to estimate extravascular lung water easily mastered by nephrologists that help to quantify lung congestion by counting B-lines per lung area unit (Comet line scoring). The "Lung water by ultrasound guided treatment to prevent death and cardiovascular complications in high risk ESRD patients with cardiomyopathy" study has shown the clinical value of LUS in the management of HD patients at high cardiovascular risk[212,213] (Figure 3).

A further tool to reduce intradialytic hemodynamic stress is the development of wearable non-pervasive methods for continuous blood pressure monitoring. This would allow detection of subtle changes in blood pressure to prompt interventions such as reduction of ultrafiltration rate to prevent hypotension. Recent work using additional pressure sensors placed on dialysis lines to derive blood pressure without the need for additional equipment attached to the patient, shows promise in this regard[214,215]. Considering the high cardiac mortality risk of HD patients (10 to 100 times greater than the general population)[216], it appears of utmost importance to pay closer attention to cardiovascular monitoring to ensure early and appropriate intervention for improving outcomes[49]. Interestingly, new remote technologies or so-called connected iHealth devices offer convenient new tools for monitoring high risk HD patients during the interdialytic period in a fully automated and ambulatory mode[217]. Detection of clinical significant arrhythmias would be one important functionality, as shown in recent studies[146,218] (Figure 3).

FUTURE DEVELOPMENT OF HD AND RENAL REPLACEMENT THERAPY

In order to reduce dialysis associated morbidity and to improve patient experience, three main approaches should be proposed and explored.

Designing and adapting HD treatment schedule to individual patient needs, tolerance, and risks

Aside from the introduction of more flexible treatment schedules, recent studies have also shown the potential interest of stratifying patients according to their risks at short or medium term outcomes[219, 220]. A better understanding of patient risks could help physicians to prescribe more appropriate and individualized therapy. Also, scoring systems could be tested as supports to alter specific treatment prescription features in an attempt to reduce early mortality of ESKD patients transitioning to dialysis.

Using automated systems embedded in intelligent dialysis machines

The technology relies on the combination of patient biologic sensors coupled to a feedback control loop and governed by adaptive algorithms embedded in the dialysis machine. The first example is the sodium control module that has been assessed and validated in clinical trials[72,221]. Using continuous conductivity cell measurements on inlet and outlet dialysate flow, an embedded algorithm controls plasma sodium concentration changes (*i.e.*, tonicity) and allows precise monitoring of plasma sodium concentration and sodium mass removal occurring within dialysis session. Interestingly, sodium mass transfer and plasma tonicity rely on an automated and self-adapting function that follows medical prescription setting. Further outcome based studies are needed to establish clinical benefits to patients and the device's clinical added value[222].

Combined use of connected iHealth devices, advanced analytics, and artificial intelligence will be able to support medical decision making and to predict future outcome

Personalized medicine relying on iHealth trackers, advanced analytics, and artificial intelligence (artificial neuronal networks and machine learning) may allow identification of patients at increased risk. In this respect, the use of such tools will be able to support physician decision-making for individual patients to select the most appropriate treatment modality or suitable technical approach (*i.e.*, ultrafiltration rate and dialysate sodium) to reduce cardiovascular burden[223,224]. Furthermore, iHealth trackers and machine learning support may also be applied to continuous vital signs monitoring and other intra-dialytic hemodynamic variables. The ultimate goal is to detect or predict the occurrence of future clinical events with sufficient precision and time to intervene. Such iHealth trackers seem particularly attractive to monitor arrythmias and maybe to help prevent sudden cardiac death[217]. In brief, the paradigm of precision medicine appears particularly relevant to renal replacement therapy for designing a personalized, more effective, better tolerated, and more acceptable HD treatment[225].

CONCLUSION

In this in-depth review, we have summarized factors that are implicated in the cardiovascular and multi-organ morbidity associated with conventional short intermittent HD treatment schedules. Hidden risks result mainly from the conjunction of two main phenomena: First, the intermittent nature of the treatment that is responsible for an unphysiologic profile (illustrated by peaks and troughs reflecting fluctuation of internal milieu composition) and a multifactorial systemic stress; second, the incomplete correction of uremic metabolic abnormalities that may be summarized as "residual syndrome". Such systemic stress induced by HD treatment is likely implicated in the poor dialysis tolerance and end-organ injury contributing to the DS syndrome. We summarize this cascade of events as the dialysis stress storm and sickness syndrome (D4S) and propose that D4S may act as a negative disease modifier of patient outcome.

Mitigating cardiovascular burden in HD requires further concerted actions to change the treatment paradigm. Such an approach will have multiple targets that should ideally include optimizing hemodynamic management both during the inter- and intra-dialytic phase, enhancing renal replacement therapy efficacy, and personalizing treatment schedule with use of new monitoring tools.

FOOTNOTES

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Country/Territory of origin: Germany

ORCID number: Bernard Canaud 0000-0001-6854-2816; Jeroen P Kooman 0000-0003-0257-8650; Nicholas M Selby 0000-0003-0351-8326; Maarten Taal 0000-0002-9065-212X; Andreas Maierhofer 0000-0001-8257-7898; Pascal Kopperschmidt 0000-0003-3652-9312; Susan Francis 0000-0003-0903-7507; Allan Collins 0000-0002-2687-4414; Peter Kotanko 0000-0003-4373-412X.

Corresponding Author's Membership in Professional Societies: Francophone Society of Nephrology, Dialysis and Transplant; ERA - EDTA; ISN; American Society of Nephrology.

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Retrospective Cohort Study

Clinical presentation and outcomes of chronic dialysis patients with COVID-19: A single center experience from Greece

Dimitra Bacharaki, Minas Karagiannis, Aggeliki Sardeli, Panagiotis Giannakopoulos, Nikolaos Renatos Tziolos, Vasiliki Zoi, Nikitas Piliouras, Nikolaos-Achilleas Arkoudis, Nikolaos Oikonomopoulos, Kimon Tzannis, Dimitra Kavatha, Anastasia Antoniadou, Demetrios Vlahakos, Sophia Lionaki

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Dimitra Bacharaki, Minas Karagiannis, Aggeliki Sardeli, Panagiotis Giannakopoulos, Vasiliki Zoi, Nikitas Piliouras, Kimon Tzannis, Sophia Lionaki, Nephrology Unit, Department of Internal Medicine, "Attikon" University Hospital, Chaidari 12462, Greece

Dimitra Bacharaki, Minas Karagiannis, Aggeliki Sardeli, Panagiotis Giannakopoulos, Nikitas Piliouras, Kimon Tzannis, Dimitra Kavatha, Anastasia Antoniadou, Demetrios Vlahakos, Sophia Lionaki, Medical School, National and Kapodistrian University of Athens, Athens 15772, Greece

Nikolaos Renatos Tziolos, Dimitra Kavatha, Anastasia Antoniadou, Department of Internal Medicine, "Attikon" University Hospital, Chaidari 12462, Greece

Nikolaos-Achilleas Arkoudis, Nikolaos Oikonomopoulos, Department of Radiology, "Attikon" University Hospital, Chaidari 12462, Greece

Corresponding author: Dimitra Bacharaki, MD, PhD, Consultant Physician-Scientist, Nephrology Unit, Department of Internal Medicine, "Attikon" University Hospital, Rimini 1, Chaidari 12462, Greece. bacharaki@gmail.com

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is still a menacing pandemic, especially in vulnerable patients. Morbidity and mortality from COVID-19 in maintenance hemodialysis (MHD) patients are considered worse than those in the general population, but vary across continents and countries in Europe.

AIM

To describe the clinical course and outcomes of hospitalized MHD patients with COVID-19 in a retrospective observational single center study in Greece.

METHODS

We correlated clinical, laboratory, and radiological data with the clinical outcomes of MHD patients hospitalized with COVID-19 during the pandemic. The diagnosis was confirmed by real-time polymerase chain reaction. Outcome was determined as survivors *vs* non-survivors and "progressors" (those requiring oxygen supplementation because of COVID-19 pneumonia worsening) *vs* "non-

progressors".

RESULTS

We studied 32 patients (17 males), with a median age of 75.5 (IQR: 58.5-82) years old. Of those, 12 were diagnosed upon screening and 20 with related symptoms. According to the World Health Organization (WHO) score, the severity on admission was mild disease in 16, moderate in 13, and severe in 3 cases. Chest computed tomography (CT) showed 1-10% infiltrates in 24 patients. Thirteen "progressors" were recorded among included patients. The case fatality rate was 5/32 (15.6%). Three deaths occurred among "progressors" and two in "non-progressors", irrespective of co-morbidities and gender. Predictors of mortality on admission included frailty index, chest CT findings, WHO severity score, and thereafter the increasing values of serum LDH and D-dimers and decreasing serum albumin. Predictors of becoming a "progressor" included increasing number of neutrophils and neutrophils/lymphocytes ratio.

CONCLUSION

Patients on MHD seem to be at higher risk of COVID-19 mortality, distinct from the general population. Certain laboratory parameters on admission and during follow-up may be helpful in risk stratification and management of patients.

Key Words: COVID-19; SARS-CoV-2; Dialysis; Greece; Clinical course; Outcome

Core Tip: Maintenance hemodialysis patients, a group of patients with presumed high mortality, have been reported to experience worse outcomes of coronavirus disease 2019 (COVID-19), compared to the general population internationally. However, there is a considerable variation in the reported rates of disease remission and death between different continents and countries. In this article, we present the outcomes of 32 patients on chronic dialysis who became positive for COVID-19 in the era before vaccines became available.

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INTRODUCTION

Background/rationale

Nearly two years have elapsed after the pronouncement of the novel coronavirus disease 2019 (COVID-19) on March 11, 2020 by the World Health Organization (WHO) as a global pandemic, following its first recognition in Wuhan, China in December 2019[1]. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is manifested in the majority of cases with symptoms related to the upper respiratory system or with development of mild pneumonia in 81% of cases[2]. Only 15% of infected patients develop severe lung disease, requiring oxygen support, while 5% of them progress to critical disease with complications, such as respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and multiorgan failure[3-4]. A dysfunctional as opposed to healthy host immune response is supposed to play an important role for the final outcome[5]. Patients prone to the severe form of the disease are considered to be elderly, and those with co-morbidities including diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, obesity[6-7], and chronic kidney disease, although at first not included[8]. Regarding patients with end-stage kidney disease (ESKD) who are maintained with hemodialysis or peritoneal dialysis, results from the ERACODA collaboration (the European database collecting clinical information of patients on kidney replacement therapy with COVID-19) revealed some peculiarities compared to the general population, *i.e.*, prevalent co-morbidities like hypertension, diabetes mellitus, coronary artery disease, heart failure, and chronic lung disease did not emerge as independent risk factors for mortality [6]. Notably, the aforementioned co-morbidities are highly prevalent in patients with chronic kidney disease, which is itself considered by default an independent risk factor for increased cardiovascular

and all-cause mortality[9-10]. Yet, some studies have reported increased mortality in ESKD patients with COVID-19[11-12], where others have concluded that these patients are somehow being "protected" from the severe form of COVID-19[13-14]. The reported death rates vary substantially across countries [15] and thus, genetic factors have been implicated to play a role in the development of the severe form of the disease[16].

Objectives

A cohort of patients with COVID-19 and ESKD on dialysis, who were admitted in our hospital during the pandemic, were studied, attempting to identify potential differences in terms of the clinical presentation and outcome of COVID-19 compared to the general population. We also searched for distinctive features (clinical, radiological, or laboratory) that could serve as predictors in order to recognize patients at high risk for COVID-19 adverse outcome.

MATERIALS AND METHODS

Study design

This is an observational, analytical, retrospective cohort study which took place in a single center from Greece. It was approved by the Scientific Committee of the Hospital.

Setting

The study included maintenance hemodialysis (MHD) patients, who were admitted in our hospital from April 23, 2020 till February 3, 2021 and were followed until death or release from hospital. All data were retrospectively collected from patients' electronic records and medical charts and included demographics, clinical features, laboratory and radiological data, treatment schemes, clinical course, and outcome.

Participants

All included patients provided signed informed consent, were ≥ 18 years old, had COVID-19 confirmed by polymerase chain reaction (PCR) test within the last 5 d prior to admission, and were on MHD for more than 3 mo. The exclusion criteria were patients with COVID-19 with acute kidney injury undergoing temporary hemodialysis, and MHD patients who were hospitalized with other types of pneumonia (non-related to SARS-CoV-2), active cancer, or autoimmunity. The PCR test was performed either because of symptoms, which might be attributed to COVID-19, or in case of a history of exposure to an infected patient or working personnel, or as a regular routine screening test.

Variables

Diagnosis of COVID-19 was confirmed by positive throat-swab specimens for SARS-CoV-2 using the PCR methodology, as has been described[17]. Symptoms, if present, were recorded.

Regarding clinical presentation, each patient was classified at the time of admission, according to the classification of WHO for COVID-19 severity (mild, moderate, severe, and critical disease) as described previously[4]. Accordingly, the disease was characterized as mild if there was absence of pneumonia or hypoxia, moderate if there were clinical signs of pneumonia with oxygen saturation (SatO2) > 90%, and as severe if the patient had one or more of the following: Respiratory rate > 30/min, respiratory distress, or SatO2 < 90%. The disease was determined as critical in case of acute respiratory distress syndrome, sepsis, or septic shock (Supplementary Table 1). In addition, at the time of admission, all patients were scored for their status of frailty, using the 9-point frailty scale, as previously described[18].

Regarding the clinical course, patients were grouped based on worsening or not of COVID-19 pneumonia, as follows: Those who required oxygen supplementation (for the first time, or amplification of previous) because of worsening of COVID-19 pneumonia at the time of admission, at discharge, or before death, were categorized as "progressors", while those who remained in stable clinical condition were categorized as "non-progressors" or "stable".

Regarding the final outcome (death or release from hospital), patients were grouped into a survival group and a non-survival (deceased) group. In case of death, the precise cause was recorded and characterized as COVID-19 related or not. The case fatality rate (CFR) was calculated according to previous reports[19]: The number of deaths attributed to the disease were divided by the number of diagnosed cases and multiplied by 100. Since causes of death in COVID-19 patients have been reported to differ between MHD patients and the general population[12], we recorded the CFR as the total number of deaths in COVID-19 patients but also distinguished COVID-19 related deaths attributed to respiratory failure from SARS-CoV-2 pneumonia *vs* non-related to COVID-19, *i.e.*, attributed to other causes, in patients with no respiratory worsening.

Data sources/ measurement

Information regarding the past medical history of patients was recorded from their medical charts

including the presence of all comorbidities such as hypertension, diabetes mellitus, coronary artery disease, heart failure, and chronic lung disease.

Laboratory data: Routine blood examinations included complete blood count, coagulation profile, inflammatory markers [*i.e.*, C-reactive protein (CRP) and ferritin], and serum biochemistry (renal and liver function and albumin). The data were recorded from the day of admission till death or release from hospital. Thus, we had the opportunity to study the kinetics of certain laboratory parameters that have emerged as prognostic markers in the general population[20] including neutrophils to lymphocytes ratio (NLR), lymphocytes, lactate dehydrogenase (LDH), CRP, ferritin, Il-6, D-dimers, troponin, albumin, and white blood cells (WBC). Specifically, we recorded the maximal value (or lowest in parameters such as albumin) in the time interval between admission and the 10th day and calculated the increase as a percentage from admission to the highest (or lowest) value of 10 d by dividing this difference with the value at admission.

Radiology data: All patients with COVID-19 underwent a computed tomography (CT) scan of the chest on admission, as per hospital protocol for COVID-19. All CT scans performed in COVID-19 patients were conducted using a Philips Brilliance 64 CT scanner with a 1 mm slice thickness and a high-resolution CT algorithm. Typically, a non-contrast chest CT scan was performed, with images being obtained during end-inspiration breath hold. Imaging disease extent/severity was estimated according to the COVID visual assessment scale (CoVASc), which is a visual assessment scale that roughly estimates the percentage of pulmonary parenchyma affected by COVID-19, as seen on chest CT, when both lungs are evaluated as a whole (0%, 1%-10%, 11%-25%, 26%-50%, 51%-75%, and > 75%)[21].

Bias

Since this a single center study, there was no bias regarding management. Since COVID-19 presents with stages of evolution[20], in order to overcome potential bias of delayed admission, we recorded and present mean time to admission when indicated.

Treatment scheme

By February 2021, Greece had experienced three waves of COVID-19 pandemic, March to April, September, and December 2020. Admitted patients were evaluated from the infectious disease department who decided about the therapeutic protocol based on the clinical picture and the available international therapeutic data. Five patients, who were admitted during the 1st wave, were mildly symptomatic, without severe pneumonia. They received hydroxychloroquine plus azithromycin as per infectious department protocol[22]: A loading dose of 200 mg of hydroxychloroquine at day 1, followed by 100 mg twice per day for 5 d and azithromycin 500 mg daily for 5 d.

During the 2nd and 3rd waves, the aforementioned protocol for mild disease was abandoned, as data questioned its efficacy[23]. Admitted patients requiring supplementary oxygen due to COVID-19 pneumonia to maintain SaO2 > 93%, received 6 mg intravenous dexamethasone for up to 10 d or until discharge, if sooner. Based on clinical judgment for concurrent microbial pneumonia, patients receiving dexamethasone were also prescribed azithromycin at a dose of 500 mg on day 1, and 250 mg on the following 4 d. An electrocardiograph to exclude long QT was performed in advance for both hydroxychloroquine and azithromycin prescription. Low molecular weight heparin was prescribed at a prophylactic dose in all admitted patients at a dose of 3500 benzaparin (body weight > 60 kg) and 2500 IU (body weight < 60 kg). On dialysis day, it was given during the dialysis session. Patients who experienced an incident thromboembolic event or those who were highly suspected to have thromboembolic disease were managed with therapeutic doses of anticoagulant therapy.

Dialysis scheme

Hemodialysis was performed in an isolated room, regularly three times per week, according to the related practice guidelines as described by others[24]. Blood access status was regularly recorded, as well as events necessitating intervention (hypokalemia, hypotension, and thrombosis).

Statistical analysis

Patients' data were analyzed on an exploratory basis. Continuous variables are summarized with the use of descriptive statistical measures [median and interquartile range (IQR; 25th, 75th percentile)], and categorical variables are displayed as frequency tables (*n*, %). Statistical tests used to check univariate associations between categorical or continuous variables and outcomes were Pearson's chi-squared test, Fisher's exact test, *t*-test, or Wilcoxon rank-sum test as appropriate. Box plots are used to visualize the laboratory data at admission and at their highest/lowest value. The level of 5% was used for statistical significance. All statistical analyses were performed using STATA/SE 16.1 software (Copyright 1985–2019; Stata Corp LP, College Station, TX, United States).

RESULTS

Participants

Of 40 patients who were eligible to be included in the study, 32 were finally included, since two patients were discharged from hospital in less than 5 d, one had been diagnosed with COVID-19 for more than a week, one had active cancer, one had active autoimmune disease, one had been on hemodialysis for less than 3 mo, and two had acute on chronic kidney disease, necessitating hemodialysis only temporally.

Descriptive data

The study included 32 patients on MHD, who were infected with SARS-CoV-2, were diagnosed by nasopharyngeal PCR, and were hospitalized for more than 10 d until discharge or death. Five of them were diagnosed during the first wave and the rest presented during the second and third waves. As shown in Table 1, they had a median age of 75.5 (IQR: 58.5-82) and 17 of them were males (53.1%). The prevalent co-morbidity was arterial hypertension found in 20 (62.5%) patients, followed by diabetes mellitus in 10 (31.3%). The median number of comorbidities was 3 (IQR: 2-3.5). The median frailty index was 3 (IQR: 2-5). Diagnosis was made by routine screening in 12 (37.5%) cases or because of symptoms suggestive of COVID-19 (62.5%). The symptoms included fever in 13 (65%) patients, upper respiratory symptoms (dry cough and dyspnea) in 6 (30%), and diarrhea in 1 (5%). None of the patients reported anosmia, while one (3.125%) reported ageusia. In order to exclude potential confounders of delayed admission to the hospital, we recorded the median time to admission. It was 2 d (IQR = 1-3, min = 0, max = 5) for symptomatic patients and 1 d (IQR = 0.5-1) for those diagnosed after routine screening.

According to the WHO severity score on admission, 50% of patients[16] presented with mild and 40.6% with moderate disease[13], while severe disease was observed only in three (9.4%) patients. No patient presented with critical disease.

Regarding radiological characteristics on admission, all except one patient, had a chest CT scan on admission. The patient without chest CT was asymptomatic and had normal chest X-rays on admission. The majority of patients [24 (77.4%)] had a CoVASc score of 0%-10%, *i.e.*, low grade pulmonary infiltrates, corresponding to mild and moderate WHO. Of the remaining seven patients with a CoVASc score > 10%, four had a score of 11%-25%, corresponding to moderate disease, two had a score of 26%-50% and one had a score of 51%-75%, corresponding to severe WHO disease group.

Comparison of patients who were admitted with mild *vs* those with moderate/severe disease (16 patients in each group) (Table 2) revealed that they differed only regarding the presence of symptoms. Asymptomatic patients were mostly in the mild group[11,16] *vs* 1/32 in the moderate group with statistical significance (P = 0.001). Age, frailty index, sex, number of comorbidities, and CoVaSc CT score were not statistically different.

Treatment scheme

Sixteen (50%) patients received therapy for COVID-19, including hydroxychloroquine plus azithromycin. Thirteen (40.6%) patients received dexamethasone plus azithromycin. One patient developed severe COVID-19 pneumonia, despite dexamethasone treatment, and was further deteriorated to severe acute respiratory distress syndrome. He was treated with tocilizumab (8 mg/kg once), and he was gradually improved and was discharged with no need for oxygen support. Broad spectrum antibiotics were prescribed in case of suspected superimposed bacterial pneumonia, or other in-hospital infections in 17 (53.1%) cases.

Characteristics related to MHD

The mean time in dialysis prior to COVID-19 was 4 years. The most prevalent primary disease was arterial hypertension. Arteriovenous access was arm fistula in 15 (46.8%) patients, graft in 2 (6.2%), and ventral venous catheters in the rest. Potassium supplementation during dialysis was required in 12 (37.5%) patients. Hypotensive episodes were recorded on 17 (53.1%) patients. Thromboembolic events associated with access were recorded in 5 (15.6%) patients.

Outcome data

"Progressors" *vs* "non-progressors": Thirteen (40.6%) patients experienced progression of COVID-19, manifesting as respiratory deterioration, which occurred 7-10 d after documentation of the infection (Table 1). "Progressors" (eight males and five females) had a median age of 78 (IQR: 75-82) years and a median frailty index 3 (IQR: 2-5). Eight of them (66.7%) had very limited findings on CT of the chest on admission (< 10%) and four patients had moderated findings (> 10%). Five (38.5%) patients presented with mild disease on admission, five (38.5%) had moderate disease, and three (23.1%) were asymptomatic. The median time to admission was similar between "progressors" [median: 1 (IQR: 1-3) d] and "non-progressors" [median: 1 d (IQR: 1-2) (P = 0.68)]. Ten (76.9%) of "progressors" were diagnosed with symptoms (76.9%) while three by screening.

Comparison between "progressors" *vs* "non-progressors" did not reveal any difference in terms of age, gender, or frailty. Those patients who did not progress tended to have a higher percentage of mild disease, but it did not differ statistically form that of "progressors" (P = 0.095). Compared to stable

Table 1 Comparison of demographics and baseline characteristics of patients grouped by outcome

	Total patients, *n* (%)	Survivors, *n* (%)	Non-survivors, *n* (%)	*P* value	Non-progressors, *n* (%)	Progressors, *n* (%)	*P* value
Characteristic	32 (100)	27 (84.4)	5 (15.6)		19 (59.3)	13 (40.6)	
Male	17 (53.1)	16 (59.3)	1 (20)	NS	9 (47.4)	8 (61.5)	NS
Female	15 (46.9)	11 (40.7)	4 (80)		10 (52.6)	5 (38.5)	
[1]Age	75.5 (58.5-82)	75 (56-82)	76 (75-80)	NS	70 (53-82)	78 (75-82)	NS
[1]Frailty index	3 (2-5)	3 (2-5)	7 (3-8)	< 0.05	3 (2-5)	3 (2-5)	NS
CT (%)				< 0.01			NS
0-10%	24 (77.4)	23 (88.5)	1 (20)		16 (84.2)	8 (66.7)	
> 10%	7 (22.6)	3 (11.5)	4 (80)		3 (15.8)	4 (33.3)	
WHO				0.05			NS
0	16 (50)	15 (55.6)	1 (20)		11 (57.8)	5 (38.5)	
1	13 (40.6)	11 (40.7)	2 (40)		8 (42.1)	5 (38.5)	
2-3	3 (9.4)	1 (3.7)	2 (40)		0 (0)	3 (23)	
Diabetes	10 (31.3)	7 (25.9)	3 (60)	NS	7 (36.8)	3 (23.1)	NS
Hypertension	20 (62.5)	18 (66.7)	2 (40)	NS	11 (57.8)	9 (69.2)	NS
[1]Number of comorbidities	3 (2-3.5)	3 (2-4)	3 (2-3)	NS	3 (1-4)	3 (2-3)	NS
Symptoms				NS			NS
Fever	13 (65)	10 (62.5)	3 (75)		8 (80)	5 (50)	
Respiratory	6 (30)	5 (31.2)	1 (25)		1 (10)	5 (50)	
Diarrhea	1 (5)	1 (6.3)	0 (0)		1 (10)	0 (0)	
COVID diagnosis				NS			NS
With symptoms	20 (62.5)	16 (59.3)	4 (80)		10 (52.6)	10 (76.9)	
Screening	12 (37.5)	11 (40.7)	1 (20)		9 (47.4)	3 (23.1)	

[1]Median (interquartile range).
WHO severity score: 0: Mild disease, 1: Moderate disease, 2: Severe disease.
CT: Computed tomography; NS: Non-significant; COVID: Coronavirus disease.

patients, "progressors" tended to be older (median age: 78 *vs* 70, $P = 0.087$), and experienced more respiratory symptoms on initial presentation (50% *vs* 10%, $P = 0.14$).

Survivors *vs* non-survivors: Overall (Table 1), 27 (75.8%) patients were discharged from hospital, after a median hospitalization time of 22 d (IQR = 15-35). Five patients died (Table 2) (CFR 15.6%) within a median time to death of 35 d (IQR: 24-35). The deceased *vs* survivors differed in being more frail (median: 7 *vs* 3, $P = 0.016$), with worse WHO severity ($P = 0.05$) and worse CT findings on admission ($P = 0.005$).

There were three cases of COVID-19 related death (respiratory failure), all among "progressors" (23%). Two of them died after they had been intubated and transferred to the intensive care unit. Two of them were female and one was male, aged 75-80 years old, with a frailty index on admission of 2.8 and 3, respectively. All three dying from COVID-19 related death had a CoVASc score > 10% on chest CT and they had moderate (2 cases) or severe (1 case) disease on admission.

Two deaths, non-related to COVID-19, were recorded in female patients, aged 70 and 85 years with recorded time to death being in 24 and 35 d, respectively, from admission. The frailty index was 7 in both cases and the cause of death was sudden cardiovascular event and aspiration, respectively.

Laboratory analysis: Laboratory parameters on admission did not show any statistically significant association with outcome, either death or progression of COVID-19 (Table 3). There was a trend, though, for "progressors" and non-survivors to present with lower levels of lymphocytes, and higher CRP and NLR values, compared to patients who remained stable thereafter, and the survivors. "Progressors" had also a trend for higher numbers of neutrophils and level of serum ferritin values on

Table 2 Comparison of characteristics of patients grouped by World Health Organization coronavirus disease 2019 severity

Disease severity	Mild (16/32)	Moderate/severe (16/32)	*P* value
	Median (IQR)	Median (IQR)	
Age (yr)	77.5 (54.5-84.5)	75.5 (67.5-78.5)	NS
Frailty index	3.5 (2-5)	3 (2-4.5)	NS
Co-morbidities	3 (1-3)	3 (2-4)	NS
Men, *n* (%)	7 (43.8)	10 (62.5)	NS
Women, *n* (%)	9 (56.2)	6 (37.5)	
Screening, *n* (%)	11 (68.8)	1 (6.3)	< 0.01
Symptomatic, *n* (%)	5 (31.2)	15 (93.7)	
CT infiltrates			NS
0-10%	13 (86.7)	11 (68.8)	
> 10%	2 (13.3)	5 (31.2)	
COVID death, *n* (%)	0 (0)	3 (21.4)	NS
Non-COVID death, *n* (%)	1 (7.1)	1 (9.1)	NS
COVID progression, *n* (%)	5 (31.3)	8 (50)	NS

CT: Computed tomography; NS: Non-significant; COVID: Coronavirus disease.

admission. (Table 3, Figures 1 and 2).

We found a statistically significant difference between "progressors" and stable patients, regarding the highest 10-d value of neutrophils [6800 (IQR: 5300-9600) *vs* 4600 (IQR: 2700-5600), $P = 0.018$], the highest value of NLR [13.4 (IQR: 7.7-26.3) *vs* 3.3 (IQR: 2-5.3) $P = 0.001$], and the related percentage increase [235.9 (IQR: 18.4-394.4) *vs* 2.5 (IQR: -31.5-25.9), $P = 0.005$].

Comparison between non-survivors *vs* survivors, revealed that they differed significantly regarding the highest value of LDH [median: 313 (IQR: 272-330) *vs* 225.5 (IQR: 183-256), $P = 0.028$] and its percentage increase [89.7% (IQR 5-97.5) *vs* 5.6% (-13.8-25.2) increase, $P = 0.039$]. Additionally, non-survivors had the lowest 10-d value of albumin [median: 2.9 g/dL (IQR: 2.7-3.1] *vs* [3.5 (IQR: 2.9-3.7), $P = 0.028$], and the highest 10-d value of D-dimers [median 3503 ng/mL (3447-5032) *vs* 1624 (1073-2526), $P = 0.011$]. Troponin levels did not show any statistically significant difference neither in deceased patients nor in progressors.

DISCUSSION

Key results

This article analyzes our experience with COVID-19 in a cohort of 32 patients on MHD during an 11-m period before COVID-19 vaccination was available. The aim of the study was to describe the clinical characteristics of the disease at presentation and its outcomes in this group of patients, and look for distinctive features predicting outcome. According to our findings, age, gender, and the presence of co-morbidities did not show any statistical difference between survivors and non- survivors and between "progressors" and "non- progressors". On the contrary, the frailty index, the WHO severity score, and the CoVASc score on admission seemed to matter, since they differed statistically between survivors and non-survivors. In terms of laboratory parameters at the time of admission, a more "inflamed" laboratory profile (CRP and NLR) and lower lymphocytes were shown to be a potential alarm for adverse clinical evolution ("progressors and deceased patients"). However, the kinetics of inflammation markers (NLR and neutrophils) over 10 d of hospitalization were able to distinguish with statistical significance "progressors" *vs* "non-progressors". In addition, the kinetics of LDH and D-dimers (increase) and albumin (decrease) were able to distinguish with statistical significance non-survivors from survivors.

Interpretation

The vast majority of MHD patients in our study (90. 6%) presented with mild (50%) or moderate (40.6%) severity of COVID-19, according to the WHO classification system. Apart from symptoms, being statist-

Table 3 Comparison of laboratory measurements between patients with different coronavirus disease 2019 outcomes

Variable		Survival status			Respiratory progression due to COVID-19		
	Total (*n* = 32)	Survivors (*n* = 27)	Non-survivors (*n* = 5)	*P* value	No (*n* = 19)	Yes (*n* = 13)	*P* value
	Median (IQR)				Median (IQR)		
Lymphocytes (k/μL)							
On admission	0.9 (0.8-1.4)	1 (0.8-1.4)	0.6 (5.3-1.3)	NS	1 (0.8-1.5)	0.8 (0.5-1.3)	NS
Highest value of 10 d	1.4 (1-1.7)	1.3 (1-1.7)	2.5 (1.4-3.4)	NS	1.4 (1.2-1.8)	0.9 (0.5-1.5)	NS
Increase (%)	10.4 (-2.3-51.6)	10.3 (-2.6-42.7)	60.8 (6.8-365.1)	NS	37.6 (5.4-83.2)	6.8 (-9.4-10.6)	NS
CRP (mg/L)							
On admission	19.3 (9.6-47.7)	17.2 (8.1-88.2)	22 (19.3-41.8)	NS	17.2 (8.1-41.2)	32.8 (10.6-88.2)	NS
Highest value of 10 d	55.6 (15.5-111.5)	55.2 (15.1-108)	83.5 (31.9-220)	NS	34.8 (10.6-79)	92 (31.9-149)	NS
Increase (%)	61.6 (-8.2-312.6)	54.3 (-0.9-308.8)	426.3 (-36.3-435.3)	NS	45 (-15.5-160.4)	300.9 (0-513.2)	NS
WBC (mg/L)							
On admission	5.9 (4.7-7.9)	5.9 (4.5-8)	6.2 (5.3-7.7)	NS	5.9 (4.8-7.7)	5.9 (4.2-8.8)	NS
Highest value of 10 d	7 (5.4-10.4)	7 (5.3-10)	9.4 (8-10.8)	NS	6.9 (5.3-9.4)	8 (5.9-12.6)	NS
Increase (%)	16.9 (-2.5-73.2)	15.4 (-2.9-44.5)	88.1 (21.4-103.8)	NS	15.4 (0-36.4)	74.9 (-10.1-103.8)	NS
Neutrophils (k/μL)							
On admission	4 (2.8-5.8)	4 (2.8-5.8)	3.8 (3.7-4.4)	NS	3.8 (2.5-4.7)	4.9 (3.4-6.7)	NS
Highest value of 10 d	5.3 (3.2-7.3)	4.8 (3.1-7.3)	5.6 (5.5-7.3)	NS	4.6 (2.7-5.6)	6.8 (5.3-9.6)	< 0.05
Increase (%)	19.7 (-1.8-82.9)	16.7 (-1.8-73.3)	47.6 (19.8-154.8)	NS	18.7 (3.3-39.8)	102.4 (-6.8-162.8)	NS
NLR							
On admission	4.4 (2.9-6.5)	4.1 (2.9-6.4)	5.6 (2.8-7.1)	NS	3.7 (2.6-6)	4.9 (4.1-8.2)	NS
Highest value of 10 d	5 (2.7-10.6)	4.7 (2.7-10.2)	10 (3.3-14.6)	NS	3.3 (2-5.3)	13.4 (7.7-26.3)	< 0.01
Increase (%)	17.8 (-12.8-116.1)	18.4 (-14-65.6)	6.4 (3.9-263.6)	NS	2.5 (-31.8-25.9)	235.9 (18.4-394.4)	< 0.01
Albumin (g/dL)							
On admission	3.8 (3.5-4.1)	3.8 (3.5-4.1)	3.9 (3.7-4)	NS	3.8 (3.5-4.1)	3.9 (3.5-4)	
Lowest value of 10 d	3.3 (2.9-3.7)	3.5 (2.9-3.7)	2.9 (2.7-3.1)	< 0.05	3.3 (2.8-3.7)	3.2 (2.9-3.5)	NS
Decrease (%)	12.1 (3.6-20.5)	10 (3.6-18.8)	25.6 (16.2-26.7)	NS	10 (3.6-18.8)	17.1 (7.7-20.5)	NS
Ferritin (ng/mL)							
On admission	448 (241.5-911)	459 (249-940)	408 (224-745)	NS	341 (202-940)	745 (369-904)	NS
Highest value of 10 d	1018 (445.5-1507)	1038 (428-1559)	605 (520-666)	NS	548 (295-1455)	1102 (666-1837)	NS
Increase (%)	49.3 (24.5-129.5)	54.8 (26.3-129.2)	27.5 (-21.9-146.6)	NS	30.2 (26.3.4-97.7)	129.7 (12.4-197.3)	NS
LDH (U/L)							
On admission	216 (174-285)	222 (175-276)	207 (174-298)	NS	216 (158-297)	217.5 (193-232.5)	NS
Highest value of 10 d	227 (183-273)	225.5 (183-256)	313 (272-330)	< 0.05	224 (184-256)	261 (177.5-321.5)	NS
Increase (%)	5.7 (-13.8-60.6)	5.6 (-13.8-25.2)	89.7 (5-95.7)	< 0.05	5.8 (-14.7-25.2)	5 (-11.6-89.7)	NS
Ddimers (ng/mL)							

On admission	1325 (772-2841)	1080 (772-21562349	3089 (1244-5205)	NS	1080 (732-3136)	1640 (996-2349)	NS
Highest value of 10 d	1861.5 (1215-3503)	1624 (1073-2526)	3503 (3447-5032)	<0.05	1624 (1259-3191)	2526 (1073-4134)	NS
Increase (%)	13 (-1.6-61.2)	7.3 (-1.6-41.2)	82.6 (19.1-195.8)	NS	18.5 (0-52)	1.4 (-21.3-104.3)	NS
Troponin							
On admission	72.3 (33.6-99.6)	72.9 (26.9-102)	71.4 (53-86.7)	NS	53 (25.8-84.4)	86.7 (49.8-102)	NS
Highest value of 10 d	84.6 (46.7-116)	84.4 (38.3-118)	92.6 (62-114)	NS	66.5 (29.4-108)	103 (83.2-118)	NS
Increase (%)	17.7 (2-39.6)	17.6 (1-45)	29.7 (17.3-31.5)	NS	17.6 (1-50.4)	29.7 (2.9-34.1)	NS

CRP: C-reactive protein; LDH: Lactate dehydrogenase; NLR: Neutrophils to lymphocytes ratio; WBC: White blood count/1000; NS: Non-significant.

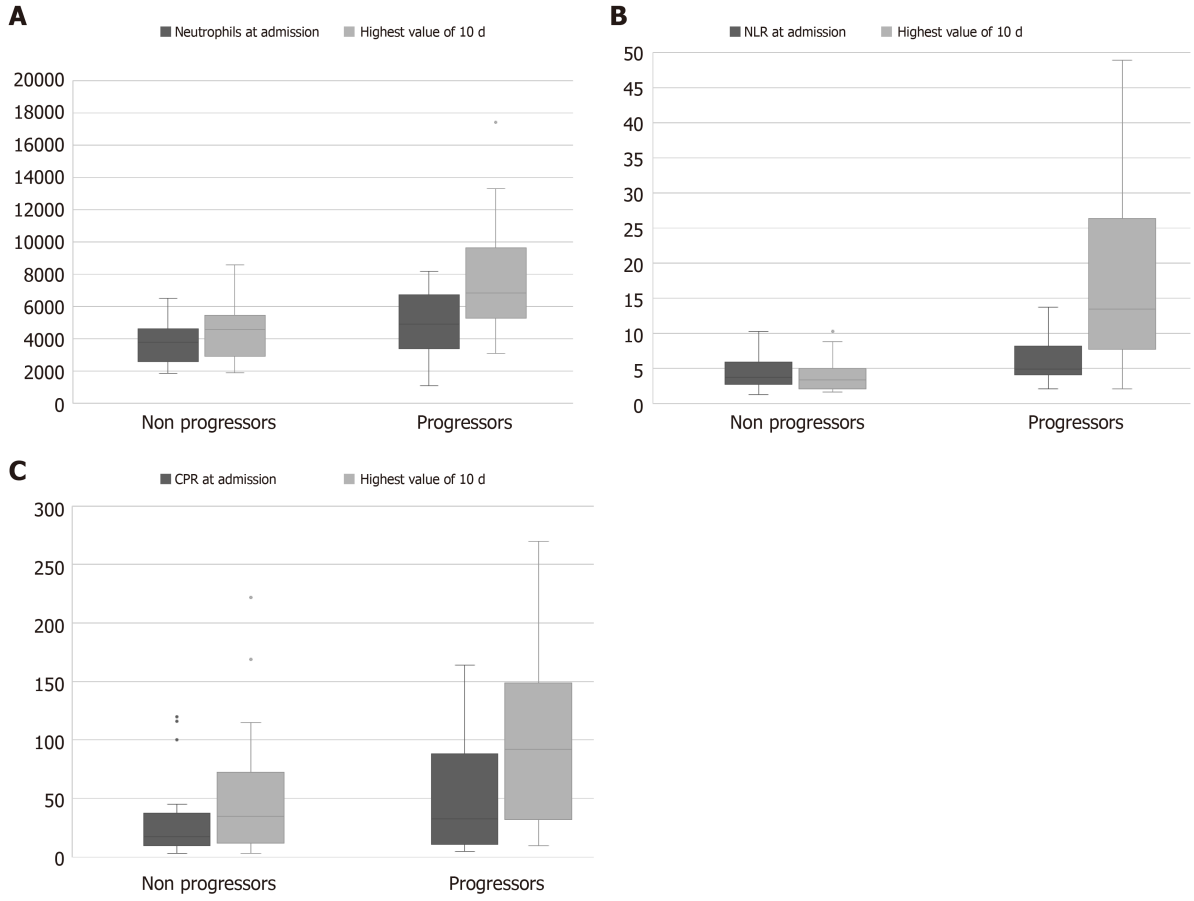

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Figure 1 Alterations of laboratory measurements from the time of admission to the highest values 10 d later between "progressors" *vs* "non-progressors" on maintenance hemodialysis with coronavirus disease 2019. A: Neutrophils count; B: Neutrophils to lymphocytes ratio; C: C-reactive protein.

ically more prevalent in moderate disease, the severity groups did not differ statistically regarding age, gender, number of co- morbidities, or CoVASc radiology data. In relation to this, a recent study which compared patients on chronic dialysis with a propensity matched cohort found that dialysis patients had a less severe COVID-19 phenotype[25]. In the present study, 12 patients were diagnosed by screening (37.5%) and 20 (62.5%) with symptoms, mainly fever (65%), respiratory symptoms (30%), and diarrhea (5%). Interestingly, no patient complained of anosmia or ageusia, in contrast to the general population, as reported by others as well[26]. Anosmia and ageusia have been attributed to the fact that angiotensin-converting enzyme II has been identified as the cellular receptor for SARS-CoV-2, which is found in the oral cavity and nasal mucosa[27,28]. However, dialysis patients have been shown to have reduced angiotensin-converting enzyme II plasma cell activity[29].

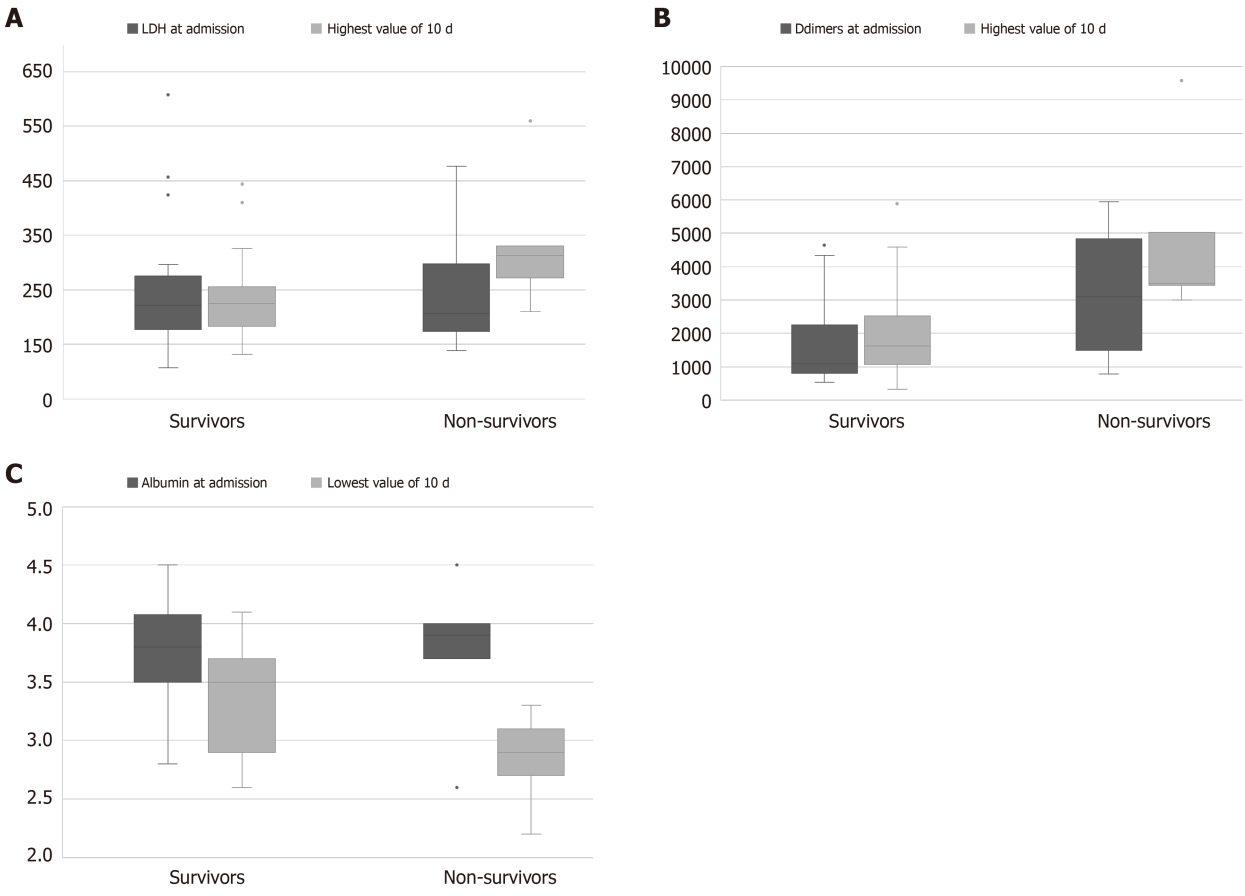

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Figure 2 Alterations of laboratory measurements from the time of admission to the highest (or lowest) values 10 d later between "survivors" *vs* "non-survivors" on maintenance hemodialysis with coronavirus disease 2019. A: Serum lactate dehydrogenase; B: D-dimers; C: Serum albumin.

Despite the relatively mild initial presentation, 40.6% of patients experienced progressive disease of the respiratory system. The CFR in our cohort was 15.5%. Four of the deaths occurred among "progressors" (30.7%), with three of them being related to COVID-19 (9.3%). Non-COVID-19 related death (sudden death and aspiration) occurred in 6.2%, one in "progressors" and one in "non-progressors". In a dialysis population of similar size from Spain[11], the CFR was reported in 30.5%. However, the Spanish cohort had worse disease status at presentation, with poor oxygen saturation (< 95%) in breathing room air observed in 22 out of 36 patients[11]. Accordingly, in a cohort study of ICU patients, the rate of death related to COVID-19 differed in dialysis patients compared to the general population, with a higher prevalence of sudden death/arrhythmia and septic shock in the dialysis population[12].

Patients on chronic dialysis have been reported to be either more vulnerable[11-12] or rather protected[13-14,25]. An international study including dialysis patients concluded that these patients were both more susceptible to severe COVID-19 disease and experienced increased mortality, although with great disparity in mortality rates[30].

In clinical practice, the most challenging question is the identification of prognostic factors, which might help clinicians to recognize those patients at high risk for disease progression and/or death. We did not find any specific clinical characteristics or radiology indexes that could discriminate "progressors" from stable patients on admission. The clinical implication, in the setting of chronic dialysis, is that even almost asymptomatic patients were candidates for disease aggravation. In the general population, the CT severity score, inflammatory markers, and older age on admission have been described as independent risk factors for short-term progression[31-32].

From the laboratory perspective, on admission there was a trend, in the "progressors" group, of lower lymphocyte count and higher NLR, CRP, and ferritin values, *i.e.*, a more inflammatory profile, as previously shown[25]. These laboratory parameters have been associated with severe COVID-19 in the general population[32-36] as well.

However, follow-up of laboratory measurements revealed that there was a statistically significant increase of neutrophils and NLR during the first 10 d, between "progressors" and stable patients. Similar findings have been reported for laboratory data on the 7th day after admission for dialysis

patients with COVID-19[11]. Also, CRP has been used in hospitalized patients with COVID-19 for disease stratification and prognostication[36]. However, in our cohort there was only a trend for the value of day 10 for the "progressors".

In terms of survival, the WHO severity score on admission, the frailty index, and the CoVAsc radiology data were shown to differ between survivors and non-survivors. Interestingly, no difference was found in clinical and radiological data on admission between "progressors" and "non-progressors". Yet, death occurred also from non-COVID-19 respiratory failure, *i.e.*, non-COVID19 related. Zeng *et al* [37] compared the annual all-cause mortality in dialysis patients during the pandemic and found that it was significantly higher in 2020 (4.89%) than in 2018 (2.55%) or 2019 (1.97%). During the COVID-19 outbreak, the mortality rate from all causes excluding COVID-19 was 2.73%, which was slightly higher than that from COVID-19 (2.16%). In our cohort, we recorded a rate of 5.9% non-COVID-19 related deaths. As has been reported[2], patients with severe underlying diseases often die with COVID-19, *i.e.*, they die of their original co-morbidities. In our cohort, as in the large ERA-CODA[6], the frailty index in contrast to co-morbidities, discriminated survivors from non-survivors patients in chronic dialysis.

None of the laboratory parameter on admission could discriminate survivors from non-survivors, except a tendency for lower lymphocytes, and higher CRP, NLR, and D-dimer values on admission, *i.e.*, a more inflammatory profile. Importantly, follow-up of the laboratory values over 10 d revealed that non-survivors differed significantly from survivors only regarding the 10th-d value of LDH and D-dimers (higher values) and the lowest 10-d value of albumin. The sequential increase of LDH has been described as a prognostic laboratory marker for severe COVID-19 in the general population[38] and dialysis patients[11,39], indicating cytokine-induced lung tissue damage[38]. Increased levels of D-dimers have also associated with adverse outcomes in COVID-19 patients both in the general population[40] and in patients on MHD[39]. Interestingly, troponin levels did not show any significant difference either in deceased patients or in "progressors". Troponin levels have been described as a predictive marker of COVID-19 mortality in the general population[33], a finding which was not confirmed in dialysis patients[39]. This is probably related to the fact that troponin levels in patients with chronic kidney disease may be related to chronic structural heart disease rather than acute ischemia[41].

Due to the small number of patients, we cannot draw any conclusions on the effect of treatment. During the 1st wave, the combination of hydroxychloroquine and azithromycin was given only in three symptomatic patients, all of whom survived. However, they had all presented with very mild disease and low CoVASc score (< 10%) although they were quite old and moderately frail. This type of treatment has not been shown to be efficient for mild and moderate COVID-19[42]. During the 2nd wave, there was no specific treatment, except the use of dexamethasone, in patients who required administration of oxygen, according to the recovery trial[43]. Azithromycin was given based on its antiviral and immunomodulatory activity[44]. No adverse effects were recorded[45]. A patient who did not respond to dexamethasone during the 3rd wave received tocilizumab for severe pneumonia and showed remarkable improvement[46].

In general, ESKD is associated with increased mortality rates compared to age-matched controls[47], especially death from cardiovascular events[48] and in the intensive care unit[49]. Since cardiovascular complications are rapidly emerging as a key threat in COVID-19 in addition to respiratory disease[50], it would be expected that this "fragile" population would be devastated by the pandemic. Patients with ESKD were shown to have the paradox of immune-activation and immune-depression[51] at the same time. For the general population, a unique immune response to SARS-CoV-2 has been described[52]. It has been proposed that ESKD patients may be rather protected for severe COVID-19, as unable to mount a cytokine hyper-active response, a cardinal feature of severe COVID-19[14]. Thus, being in chronic dialysis may not always an independent risk factor for COVID-19 adverse outcome[39].

CONCLUSION

In conclusion, herein we describe a cohort of patients on chronic dialysis who were admitted with COVID-19. A proportion of patients were diagnosed following routine testing and presented with mild disease. Absence of pneumonia or mild pneumonia was documented clinically on admission in 90.6% of patients, while CT tomography revealed infiltrates > 10% only in 13.3% of admitted patients. A CFR of 15.6%[5,32] was recorded in the whole cohort and 30.7% among "progressors". On admission a more "inflamed" profile reflected by CRP, WBC, NLR, and lower lymphocytes indicated a "hint" for upcoming progression to respiratory failure, although with no statistical significance. Clinically, statistical significance for disease progression was shown by the highest 10-d value of NLR, and its percentage increase from admission, and the highest 10-d value of neutrophils. As for survival, the frailty index, the severity stage by WHO classification, and the CoVASc score were shown statistically different on admission. Likewise, the highest 10 -d value of LDH and D-dimers and the lowest of albumin were shown to be important. Further studies are needed to unravel the immune response to COVID-19 in chronic dialysis patients and stratify the best management algorithm.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) pandemic runs as mild upper respiratory infection or being asymptomatic in 80% of infected patients, 15% develop severe lung disease, and 5% progress to respiratory failure or septic shock. Mortality ranges from 2%-50%.

Research motivation

To analyze our experience with patients with end-stage kidney disease (ESKD) on maintenance hemodialysis (MHD) with COVID-19 before the era of vaccination.

Research objectives

To identify predictors of worst outcome in patients with ESKD on MHD with COVID-19 in the era prior to vaccination, and to study all the range of clinical pictures of COVID-19 in this group of patients, including asymptomatic to severe cases all from a single center.

Research methods

This was a retrospective cohort study from a single referral center from April to February 2021. We examined the kinetics of laboratory evolution of certain parameters linked to COVID-19 pathophysiology, as potential prognostication markers of adverse outcome. Patients were scored according to the WHO severity system for COVID-19 and frailty index, besides classic demographics, and co-morbidities. A new simplified scoring system of severity (Covid Visual Assessment score, CoVAsc) was used.

Research results

Thirty-two hospitalized MHD patients with COVID-19 were studied, from admission to outcome. Although initial presentation was mild on admission regarding WHO severity (16 with mild disease, 13 with moderate, and 3 with severe) and CoVAsc score (24 patients had 0-10% lung infiltrates), the outcome was quite adverse. Approximately 40.6% of patients progressed to severe disease and 15.5% died. "Progressors" tended to have a more "inflamed" laboratory profile at the time of admission and statistically significant higher neutrophils to lymphocytes ratio during the first 10 d of hospitalization. The deceased differed from "survivors" with statistical significance as having a worse WHO severity score, frailty index, and CoVASc score and regarding the first 10-d kinetics of lactate dehydrogenase (increase), D-dimers (increase), and albumin (decrease).

Research conclusions

Traditional risk factors for adverse COVID-19 outcome including male gender and comorbidities do not seem to apply in MHD patients. Potential new clinical indicators of adverse outcome, according to our findings, include the WHO severity score, frailty index, CoVASc score, and the 10-d kinetics of certain laboratory parameters.

Research perspectives

A larger number of dialysis patients might be studied especially after vaccination and the evolving various mutations of SARS-CoV-2.

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FOOTNOTES

Author contributions: Bacharaki D designed the study and wrote the manuscript; Karagiannis M, Sardeli A, and Giannakopoulos P screened for eligibility criteria and performed data collection; Tziolos NR, Zoi N, and Piliouras N did data collection; Arkoudis NA and Oikonomopoulos N collected the radiology data and scoring system; Tzannis K analyzed the data; Kavatha D and Antoniadou A were infectious disease specialists; Vlahakos D supervised the study; Lionaki S contributed to manuscript writing and English language revision.

Institutional review board statement: The study was reviewed and approved by the Scientific Committee of our hospital.

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Country/Territory of origin: Greece

ORCID number: Dimitra Bacharaki 0000-0002-1722-2131; Minas Karagiannis 0000-0003-4081-2591; Aggeliki Sardeli 0000-0002-0597-6841; Panagiotis Giannakopoulos 0000-0001-8204-0820; Nikolaos Renatos Tziolos 0000-0001-5494-2042; Vasiliki Zoi 0000-0001-8162-0225; Nikitas Piliouras 0000-0003-4370-9338; Nikolaos-Achilleas Arkoudis 0000-0002-0783-5700; Nikolaos Oikonomopoulos 0000-0002-0862-0963; Kimon Tzannis 0000-0001-6269-5360; Dimitra Kavatha 0000-0002-1805-8695; Anastasia Antoniadou 0000-0003-0991-9198; Demetrios Vlahakos 0000-0002-8463-9607; Sophia Lionaki 0000-0003-1643-8923.

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META-ANALYSIS

Renal biopsy reports in nephritic syndrome: Update

Saeed Taheri

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Saeed Taheri, Department of Medicine, New Lahijan Scientific Foundation, Lahijan 44158-13166, Iran

Corresponding author: Saeed Taheri, MD, Doctor, Department of Medicine, New Lahijan Scientific Foundation, Hasheminejad Str, Lahijan 44158-13166, Iran. taherimd@gmail.com

Abstract

BACKGROUND

Nephritic syndrome (NiS) is a major indicator of serious renal diseases necessitating kidney biopsies for histopathological evaluations, but due to the lack of comprehensive reviews in the literature, the current understanding of the syndrome and its significance is limited.

AIM

To collect all the evidence retrievable from the literature on the diagnoses made on the renal biopsies performed for NiS as the indication to the procedure.

METHODS

A literature search was conducted to find studies reporting final diagnoses on renal biopsies in NiS patients. Data were pooled and analyzed with stratifications on age and regions. Meta-analyzes were performed using Stata v.9.

RESULTS

Overall, 26414 NiS patients from the total number of 96738 kidney biopsy diagnoses reported by 47 studies from 23 countries from all continents (except sub-Saharan Africa) were found and analyzed. NiS was the indication for renal biopsy in 21% of the patient populations across the reviewed studies. Immunoglobulin A (IgA) nephropathy was the single most frequent diagnosis in these patients (approximately 38%) followed by lupus nephritis (approximately 8%) and Henoch Schönlein purpura (approximately 7%). IgA nephropathy was the most frequent diagnosis reported for the NiS patients from the East Asia, comprising half of all the cases, and least prevalent in South Asia. Considering the age subgroups, adult (*vs* pediatric or elderly) patients were by far the most likely age group to be diagnosed with the IgA nephropathy. A myriad of such regional and age disparities have been found and reported.

CONCLUSION

As the indication for renal biopsy, NiS represents a very distinctive epidemiology of final renal disease diagnoses compared to the other major syndromes.

Key Words: Renal biopsy; Nephritic syndrome; Immunoglobulin A nephropathy;

Diagnosis; Histopathology; Epidemiology

Core Tip: Despite the extreme relevance of the renal biopsies in patients with different clinical syndromes and the final diagnoses that are being assigned to them, the current knowledge on the epidemiology of such diagnoses for nephritic syndrome is limited. This lack of understanding becomes more prominent when it comes to specific subpopulations, for example subgroups regarding age, ethnicity and global regions. This study tried to answer these questions, finding quite unprecedented, interesting, and clinically relevant findings.

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INTRODUCTION

Renal disease is a major public health concern and a subject for considerable financial and mortality burden. However, different kidney diseases generally emerge with a limited spectrum of presentations most notably proteinuria and hematuria, different constellations of which comprise specific renal syndromes. These syndromes are not considered the final diagnosis of a specific renal disease, but rather they allude to specific renal diseases of different epidemiological magnitudes. In the approach to diagnose the culprit disorders, panels of experts have introduced definite indications for renal biopsies to be performed based on the presence or absence of these clinical syndromes.

Characterized by hematuria, elevated blood pressure, edema, and decrease in urine output, nephritic syndrome (NiS) is a major indicator of serious renal diseases necessitating kidney biopsies for histopathological evaluations. According to the published statistics for the year 2017, along with the nephrotic syndrome, NiS was reportedly the 9th leading cause of death in the United States[1], and extensive data from all around the world suggests consistent risk pattern for other global regions as well. Despite the invaluable data in the literature on the subject in general, scarcity of information exists on the estimated rates of the renal disease entities diagnosed upon analysis of renal biopsies for each renal syndrome. In two previous publications, the current author addressed the abovementioned issues for nephrotic syndrome, as well as subnephrotic proteinuria[2,3]. In the current study, NiS is the subject of the systematic review.

MATERIALS AND METHODS

Searching and selecting reports for review

Figure 1 summarizes the study search and selection processes. This study aims to review the literature on the epidemiology of renal disease diagnoses made through investigating renal biopsy specimens from patients with NiS. One hundred and sixty-two reports were originally identified. After a preliminary review on the renal biopsy diagnoses (irrespective of their clinical syndromes), for studies whose data for NiS could be retrieved, 47 reports[4-50] were fully reviewed for this report. More detailed information on the methodology of this series of systematic reviews are published elsewhere, including two other reports on the epidemiology of nephrotic syndrome and subnephrotic proteinuria [2,3].

Definitions and event classifications

NiS was diagnosed when criteria for the NiS (hematuria, elevated blood pressure, decreased urine output, and edema) were fulfilled or the reports were clearly reporting either acute or chronic NiS, NiS (not otherwise specified), or NiS with nephrotic-range proteinuria (NiS-NS). Only definitive cases of NiS were included in the analysis while those with vague or equivocal data were excluded.

Renal disease diagnoses: Renal disease diagnoses included immunoglobulin A (IgA) nephropathy (Berger's Disease), Henoch Schönlein purpura (HSP), Membranous glomerulonephritis (MGN), focal & segmental glomerulosclerosis (FSGS), lupus nephritis, mesangioproliferative glomerulonephritis (MesPGN), membranoproliferative glomerulonephritis (MPGN), amyloidosis, diabetic nephropathy, crescentric glomerulonephritis (CresGN), minimal change disease (MCD), tubulointerstitial diseases

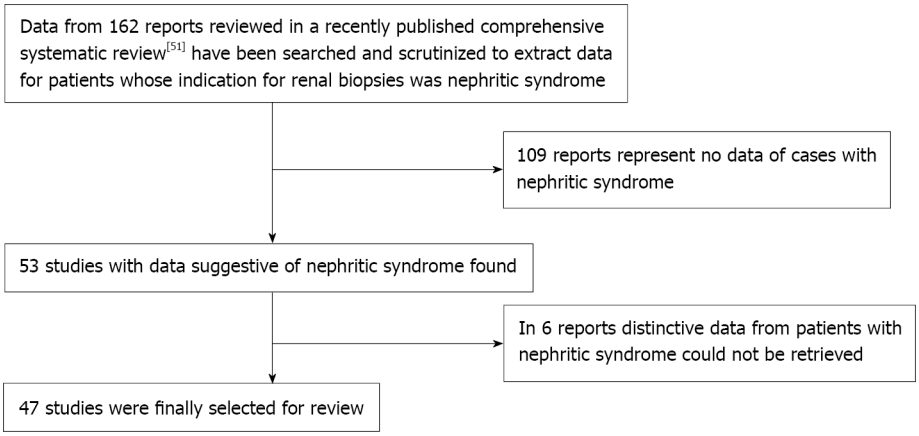

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Figure 1 Flowchart of the study selection protocol in the current review report.

(TID), vascular nephropathy, nephroangiosclerosis (NAS), hereditary nephropathy, uspecific paraproteinemias (PPEs), and uspecific proliferative glomerulonephritis (PGN). Further specifications of the diagnoses have been published previously.

World regions: World regions were defined as follows: Middle East (including Egypt, Iran, Iraq, Jordan, Kingdom of Saudi Arabia, and Kuwait), Europe (including Belgium, Croatia, Cyprus, Czech R, Poland, Portugal, Romania, Serbia, and Turkey), Latin America (including Brazil and Colombia), East Asia (including China and Japan), South Asia (including India and Pakistan), and United States-Canada-Australia (USCA) (including United States & Australia).

Age groups: Age groups were defined as '*pediatrics*', '*adults*', '*elderly*', and '*general*'. *Pediatric* group included patients 18 years of age or younger. Adults were classified for study populations older than 18 and younger than 65 years. However, some studies had inconsistent age categorizations. For example, in some studies, the lower limits of the range of patients' ages was lower than 18 years; in such cases, if the age cut was 14 years, those above the cut-off were considered as adults, but if the cut-off was less the 14, the respective study population was classified as general age. Moreover, if a study population's age range surpassed 65, the group was classified as adults. This means that in certain situations, the adult population could include elderly patients. However, if any study group contained both elderly and pediatric patients (*i.e.* less than 14 years), or the age specific epidemiology could not be definitely derived, the report was considered as a general age group. Additionally, in general, the cut-off age for defining elderly patients was 65 years; however, the subclass still included studies where the cut-off point was as low as 60 years. If the age range was less than 60 in its lower boundary, the population was classified as adults.

Trial selections for inclusion into the meta-analyses: Any study with a report of renal syndromes including definitive cases of NiS patients undergoing renal biopsies with a final diagnosis report, discretely or individually, defined for patients with each clinical syndrome (particularly NiS) were considered eligible for inclusion. No quality control criteria more than the abovementioned was used to include or exclude the studies identified.

Data extraction and quality assessment

Data extraction, data set preparations, and accuracy check (twice) were done by the author. The information extracted from each study were as follows: author, publication year, time and duration of the study, country, region/province/town, nephrology center(s), range (or mean ± SD) of age, incidence of NiS in all renal biopsy population, cases of NiS-NS, and final diagnoses of renal biopsies due to NiS. All studies that had been representing their epidemiological data for NiS and associated diagnosis without significant skewed selection in their series reports were considered eligible for entering the meta-analysis without more scrutiny in the study quality assessment.

Data synthesis and analysis

More detailed methodology of data synthesis and meta-analyses has been published previously. Final renal diagnoses have been extracted as dichotomous data (*e.g.*, MGN yes/no) and analyses have been reported as proportions with 95% confidence intervals (CIs, truncated at 0 and 1) from the extracted data. The study results were then stratified by the reports' age subgroups (*i.e.* pediatric, adult, elderly, general), and global regions of the reviewed studies (*i.e.* East Asia, Europe, Latin America, Middle East,

South Asia, United States-Australia; no report from sub-Saharan Africa). A random effect model was employed in order to pool outcome event rates using Stata v.9.0 software (StataCorp LP). Statistical heterogeneity between summary data was assessed using the Cochrane I^2 statistic. SPSS software for Windows 15.0 (SPSS Inc.) and Microsoft Excel 2013 were used wherever needed.

RESULTS

NiS as the indication for renal biopsy

Table 1 summarizes characteristics of the reviewed reports. Overall, 26414 patients with NiS have been identified from a total of 96738 patients undergoing a renal biopsy procedure reported by 47 studies from 23 countries, and their data have been reviewed and analyzed. China with 13581 NiS patients (out of a total number of 35523 cases undergone renal biopsy for any reason) contributed the largest share (51.4%) of the pooled NiS cases in this review, followed by Japan and The Czech Republic [4629 (17.5%) and 2728 (10.3%), respectively]. The frequency (95%CI) of NiS as the indication for renal biopsy was 21% (20.7-21.2) for the reviewed studies, ranging from 8% (7.5-8.5) in South Asia to as high as 36.3% (35.9-36.8) in East Asia (Figure 2A). Pediatric patients represented the lowest frequency (95%CI) of NiS as the indication for renal biopsy [7% (5.8-8.2)] while the general age group represented the highest [25.1% (24.6-25.5)] (Figure 2B). The single highest prevalence of NiS as the indication for renal biopsy in an age-region subgroup was for East Asian patients in the general-age group (Supplementary Figure 1).

Global disparity in the epidemiology of the final diagnoses made on NiS patients

Table 2 summarizes meta-analyses results of the final diagnosis epidemiology in NiS patients regarding the reports' global continental regions (Supplementary Figures 2-19 represent the forest plots). As is evident from the table and figures, the single most likely renal diagnosis to be made in NiS patients is IgA nephropathy (38.3%), followed by the lupus nephritis (8.2%) and HSP (7.1%).

There were profound disparities in the epidemiology of diagnoses regarding the reports' global regions. For example, the possibility of diagnosing unspecific PPEs in NiS patients from South Asia is about 20 times more than that for the East Asia (Table 2). MGN and FSGS were more frequently diagnosed in NiS patients from the Middle East, while in the South Asia, unspecific PPEs, as well as PGN, were by far the most likely diagnoses compared to the other world regions. In East Asia, as expected, IgA nephropathy, and MesPGN were the most likely diagnoses, together comprising over 60% of all the diagnoses made for NiS patients; whereas both entities were the least likely ones to be reported in the South Asia. Hereditary nephropathy, diabetic nephropathy, amyloidosis, and HSP were relatively more frequent in the European NiS patients, while in the USCA region, MPGN and CresGN were the relatively predominant diagnoses (Table 2).

Age disparity in the epidemiology of diagnoses

As mentioned for the world regions, there has also been disparity in the epidemiology of renal disease diagnoses in NiS patients regarding their age subgroups (Table 2 summarizes results of the respective meta-analyses, and Supplementary Figures 20-35 illustrate the forest plots). Relative to the pediatric and elderly patient groups presenting with NiS, adults were significantly more likely to be diagnosed with IgA nephropathy, HSP, and MGN. Among these, the disparity was most prominent for IgA nephropathy (only 11% and 6% of pediatric and elderly patients with NiS, respectively, were finally diagnosed with IgA nephropathy *vs* about 43% for the adults). On the other hand, pediatric NiS patients were more frequently diagnosed with lupus nephritis, MCD, hereditary nephropathy, MesPGN, and unspecific PGN, with the relatively largest disparity found with MCD. Finally, elderly patients were more likely to get diagnoses with CresGN, MPGN, TID, unspecific PPEs, diabetic nephropathy, and vascular nephropathy (including NAS), among which CresGN, unspecific PPEs and NAS were by far more frequent in this age group (*vs* the younger ones).

Another interesting observation in the study of the age-groups was that there was a trend towards higher or lower frequencies in the rates of diagnoses based on the subgroups' ages. For example, while lupus nephritis, MCD and MesPGN were decreasing in the frequency of diagnosis by advances in age (pediatrics > adults > elderly), CresGN, diabetic nephropathy, vascular nephropathy (and NAS), and unspecific PPEs were increasing by age. This observation might more strongly recommend the age effect on the occurrence of the respective renal diseases.

Final NiS diagnoses regarding age and region-double characterized subclasses

To further subclassify the patients according to their epidemiological characteristics in order to find the ones at the highest risks for each renal entity, the reports have been categorized simultaneously upon their age and world region. Supplementary Figures 36-42 summarize the results. As is depicted in Supplementary Figure 36, among all the other age and region subgroups, MGN was most frequently diagnosed in adults with NiS from the East Asia, comprising 13% of all the diagnoses. Likewise, IgA nephropathy was also most prevalently diagnosed among the East Asian adults, which together with

Table 1 Characteristics of the reviewed studies and their patient populations

Ref.	Country	Region/town	Nephrology centers	Study duration	Publication year	Age, range/mean ± SD	Total, *n*
Ossareh *et al*[4]	Iran	Tehran	Hasheminejad Kidney Center	1998-2007	2010	12–84	1407
Saberafsharian *et al*[5]	Iran	Mashhad	Ghaem and Emam Reza hospitals	2016-2018	2020	41.40 ± 16.02	860
Pakfetrat *et al*[6]	Iran	Shiraz	Shiraz University of Medical Sciences	January 2011–December 2017	2020	1- 60	1355
AlFaadhel *et al*[7]	Kingdom of Saudi Arabia	Riyadh and Jeddah	Hospital, Jeddah; Security Forces Hospital, Riyadh; College of Medicine, King Saud University, Riyadh	1998-2017	2019	18-65	1070
Al-Saegh *et al*[8]	Iraq	Kerbala	University Hospital of Kerbala	June 2010-June 2012	2013	6–50	58
Ismail *et al*[9]	Egypt	Zagazig	Zagazig University	June 2012-November 2014	2016	16-70	150
Al-Qaise *et al*[10]	Jordan	Amman	Princess Iman Research and Laboratory Center, King Hussein Medical Center	January 2005-December 2008	2010	14-75	273
Turkmen *et al*[11]	Turkey	Nation-wide data	47 centers across Turkey	May 2009-May 2019	2020	41.5 ± 14.9	4399
Sahinturk *et al*[12]	Turkey	Antalya	Antalya Training and Research Hospital	2006-2016	2019	> 65 yr	136
Hu *et al*[13]	China	Henan	The First Affiliated Hospital of Zhengzhou University	January 2009-December 2018	2020	≤ 14–60+	34,630
Su *et al*[14]	China	Changchun	First Hospital of Jilin University	January 2007-December 2016	2019	> 14 yr	2725
Wang *et al*[15]	China	Xinxiang	The First Affiliated Hospital, Xinxiang Medical University	January 1996–December 2010	2013	16–72 yr	919
Chiu *et al*[16]	Taiwan of China	Taichung	Taichung Veterans General Hospital	January 2014-September 2016	2018	48.4 ± 16.6	1445
Nair *et al*[17]	United States	Nationwide	Multiple referral centers	March 2001-December 2003	2004	60-91	533
Harmankaya *et al*[18]	Turkey	Istanbul	Bakirkoy Dr. Sadi Konuk Education and Research Hospital	2006 and 2014	2015	≥ 65	103
Sarwal *et al*[19]	India (North)	Chandigarh	Post Graduate Institute of Medical Education and Research	2007 to 2016	2019	2–94	359
Devadass *et al*[20]	India (South)	Bangalore	M.S. Ramaiah Medical College and Hospitals	2008 to 2013	2014	8 mo-78 yr	680
Das *et al*[21]	India (South)	Hyderabad	M.S. Ramaiah Medical College and Hospitals	January 1990-December 2008	2011	10-80	1849
Gupta *et al*[22]	India	New Delhi	Sir Ganga Ram Hospital	January 2011-December 2014	2018	60–85	109
Mohapatra *et al*[23]	India	Vellore	Christian Medical College and Hospital	January 1996-December 2015	2018	12.8 ± 4.9	1740
Modugumudi *et al*[24]	India	Tirupati	Sri Venkateswara Institute of Medical Sciences	May 2010-August 2012	2016	15-74	137
Khetan *et al*[25]	India	Hyderabad	Apollo Hospitals, Jubilee Hills	N/A	2018	0-15	799/958
Beniwal *et al*[26]	India	Jaipur, Rajasthan	SMS Medical College and Hospital	January 2012-December 2017	2020	60-87	230
Koshy *et al*[27]	India	Chennai, Tamil Nadu	Madras Medical Institute	January 2010-August 2016	2018	60-82	231
Maixnerova *et al*	Czech	National report	31 centers	1994–2011	2014	0-75+	10472

[28]							
Horvatic *et al*[29]	Croatia	Zagreb	Dubrava University Hospital	1996 till February 2012	2013	16-84	922
Oygar *et al*[30]	Cyprus	North Cyprus	Burhan Nalbantoglu General Hospital	January 2006-2015	2017	18-78	153
Perkowska-Ptasinska *et al*[31]	Poland	National	The Polish Registry of Renal Biopsies	2009-2014	2017	19-88	8443-951 = 7492
Pio *et al*[32]	Portugal	Porto	Hospital Geral de Santo António	January 1997-December 2008	2010	1 mo-18 yr	142
Naumovic *et al*[33]	Serbia	Belgrade	University of Belgrade	1987 to 2006	2009	16-79	1733
Volovăt *et al*[34]	Romania	Iasi	"Dr. C. I. Parhon" Hospital	2005-2010	2013	41.9 ± 2.8	514/559
Covic *et al*[35]	Romania	Timisoara	C.I. Parhon' Hospital, Iasi and 2 Dialysis and Transplantation Centers	1995–2004	2006	18–80	635
Costa *et al*[36]	Brazil (NorthEast)	Pernambuco	2 centers: Hospital das Clínicas da Universidade Federal de Pernambuco (HC-UFPE) and Instituto de Medicina Integral Professor Fernando Figueira (IMIP)	February 1998-January 2016	2017	0-60+	677/1151
Özkayin *et al*[37]	Turkey	Edirne	Trakya University School of Medicine	2005-2015	2016	1-17	100
Sugiyama *et al*[38]	Japan	National registry report	94 centers	January 2009-December 2010	2013	0-80+	7034
Sugiyama *et al*[39]	Japan	Nationwide	23 centers	1979 and 2008	2011	0–80+	2404
Malik *et al*[40]	Pakistan	Bahawalpur	Bahawal Victoria Hospital	January 2012-April 2018	2019	14-68	195
Imtiaz *et al*[41]	Pakistan	Karachi	The Kidney Center Post Graduate Training Institute	January 1996-December 2013	2017	18–88	1521
Hashmi *et al*[42]	Pakistan	Karachi	Liaquat National Hospital	January 2009-December 2013	2016	20-75	140
Mubarak *et al*[43]	Pakistan	Karachi	Sindh Institute of Urology and Transplantation	July 1995-December 2008	2011	19–85	1793
Imtiaz *et al*[44]	Pakistan	Karachi	The Kidney Center Post Graduate Training Institute	1997 to 2013	2016	0.1-17	423
Lanewala *et al*[45]	Pakistan	Karachi	Sindh Institute of Urology and Transplantation	July 1995 and June 2008	2009	4 mo-18 yr	801
AlYousef *et al*[46]	Kuwait	Sabah Al Nasser	Farwaniya Hospital	January 2013-December 2018	2020	12-90	545
Mesquita *et al*[47]	Belgium	Brussels	Brugmann University Hospital	January 1991-December 2006	2011	Adult (47 ± 19)	326
Jegatheesan *et al*[48]	Australia	Queensland	11 hospitals	January 2002-December 2011	2016	48 ± 17 (18+)	2048/3697
Prada Rico *et al*[49]	Colombia	Bogot´a, Cundinamarca	Fundaci´on Cardioinfantil, Bogot´	2007-2017	2013	11 ± 4.3	241

MGN, comprise about 60% of all the diagnoses in this subgroup of NiS patients (Supplementary Figure 37). On the other hand, FSGS was the predominant diagnosis among the European elderly (14%), followed by adults from the Middle East (13%), Supplementary Figure 38. But the single most frequent diagnosis for the Middle Eastern adults was lupus nephritis, comprising as high as 68% of all the diagnoses in these patients (Supplementary Figure 39).

Elderly Americans (54%) and elderly Europeans (34%) presenting with NiS were most likely to be finally diagnosed with the crescentric nephropathy, followed by the adult Australians and adult Europeans (17% each, Supplementary Figure 40). MPGN was the predominant diagnosis among the South Asian elderly (27%), followed by the European pediatrics (23%) and South Asian pediatrics and adults (14% each). This suggests that patients in South Asia presenting with NiS are at a substantial risk of MPGN diagnosis, irrespective of their age. But MPGN was not the only renal diagnosis frequently

Table 2 Meta-analysis of the estimated incidence (95% confidence interval) of nephropathy diagnoses for patients with nephritic syndrome

Nephropathy	Highest rate (%)	Lowest rate (%)	Pediatric (%)	Adults (%)	Elderly (%)	General (%)	NiS-NS (%)	Total (%)
MGN	M.E. 10.2 (8.1-12.3)	Eu. 2.4 (1.9-2.8)	2.5 (0.4-4.6)	7.3 (6.9-7.7)[1]	2.3 (0-5.7)	4.4 (3.9-4.8)	11.7 (6.8-16.6)	5.9 (5.6-6.2)
IgA nephropathy	E.A. 50.1 (49.3-50.8)	S.A. 9.8 (7.6-11.2)	11 (8.2-13.7)	42.6 (41.9-43.4)[1]	5.9 (2.8-8.9)	37.4 (36.4-38.3)	3.7 (0-7.8)	38.3 (37.7-38.9)
Henoch Schönlein purpura[2]	Eu. 10.7 (2.8-18.6)	S.A. 1.9 (0.5-3.2)	6.3 (3-9.6)	7.6 (7.2-8.1)[1]	-	1.2 (0-2.6)	-	7.1 (6.6-7.5)
FSGS	M.E. 11.4 (9.3-13.4)	E.A. 1.6 (1.4-1.8)	3.4 (1.7-5.1)	1.6 (1.4-1.8)	3.9 (0.9-6.8)	4.3 (3.9-4.7)[1]	19.4 (13-25.8)	2.1 (1.9-2.2)
Lupus nephropathy	L.A. 44.6 (33.7-55.5)	Eu. 4.6 (4-5.3)	12.9 (9.8-15.9)[1]	9.3 (8.9-9.8)	5.3 (1.6-8.9)	5.4 (4.7-6.1)	10.4 (6.1-14.7)	8.2 (7.8-8.6)
MCD	S.A. 4.4 (1.8-6.9)	E.A. 0.7 (0.5-0.8)	5.7 (0-12.6)[1]	0.7 (0.6-0.8)	-	1.6 (1.2-1.9)	-	0.8 (0.7-0.9)
Crescentric GN	USCA 18.9 (16.6-21.3)	E.A. 0.6 (0.2-1)	3.4 (1.7-5)	1.7 (1.3-2.2)	45.7 (36.6-54.8)[1]	6.4 (5-7.9)	-	2.3 (1.9-2.7)
MPGN	USCA. 12.9 (4.8-20.9)	E.A. 0.9 (0.7-1.1)	14.2 (11.4-17)	1 (0.9-1.2)	17.5 (12.1-22.9)[1]	4.1 (3.5-4.8)	9.2 (4.2-13.5)	1.3 (1.1-1.4)
Amyloidosis	Eu. 1.2 (0.5-1.9)	E.A. 0.8 (0.6-1.1)	0.6 (0-1.4)	0.4 (0.1-0.7)	-	2 (1.6-2.4)[1]	-	0.9 (0.7-1.1)
Diabetic nephropathy	Eu. 3.9 (3.3-4.5)	S.A. 0.8 (0-1.6)	-	1.5 (1.3-1.7)	3.1 (0-6.2)[1]	2.7 (2.2-3.2)	-	1.7 (1.5-1.9)
TID	L.A. 27.8 (4.9-50.7)	E.A. 0.6 (0.5-0.7)	3.5 (1.1-5.8)	0.6 (0.5-0.8)	6.7 (1.8-11.7)[1]	2.3 (1.3-3.3)	-	0.7 (0.5-0.8)
Vascular nephropathy	L.A. 19.3 (10.6-27.9)	M.E. 0.8 (0.1-1.5)	2.9 (0.4-5.4)	2.2 (1.9-2.4)	4.3 (1.4-7.2)[1]	3 (2.5-3.5)	-	2.3 (2.1-2.5)
Nephroangiosclerosis[2]	M.E. 20 (0-57.8)	S.A. 0.7 (0-1.6)	-	1.7 (1.5-1.9)	22.7 (9.8-35.6)[1]	3.3 (2.7-3.9)	-	1.8 (1.6-2)
Hereditary nephropathy	Eu. 3.4 (0.9-5.9)	E.A. 0.7 (0.6-0.9)	2.9 (0.8-5)[1]	0.7 (0.6-0.9)	-	-	-	0.8 (0.6-0.9)
Unspecific Proliferative GN	S.A. 34.2 (31.5-37)	E.A. 1.4 (1.2-1.6)	23.4 (20-26.9)[1]	1.6 (1.4-1.8)	20.4 (9.7-31)	11.7 (9.8-13.6)	14.1 (9-19.2)	1.7 (1.6-1.9)
MesPGN[2]	E.A. 10 (8.2-11.8)	S.A. 4.5 (3.1-5.9)	7.5 (5.2-9.7)[1]	5.3 (4.5-6.2)	-	6.2 (4.5-8)	9.2 (4.2-13.5)	5.7 (5-6.5)
Unspecific Paraproteinemia	S.A. 11.8 (1.6-22)	E.A. 0.6 (0.4-0.7)	-	0.6 (0.4-0.7)	11.8 (1.6-22)[1]	-	-	0.6 (0.4-0.7)

[1]Zero incidence rates have been omitted to report; the frequency (95% confidence interval) are those representing the highest for each diagnosis.
[2]Subsections of their abovementioned entity as described previously[2].
E.A.: East Asia; Eu.: Europe; FSGS: Focal and segmental glomerulosclerosis; L.A.: Latin America; MCD: Minimal change disease; M.E.: Middle East; MesPGN: Mesangial proliferative glomerulonephritis; MGN: Membranous glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; NiS-NS: Patients simultaneously presenting with nephritic- & nephrotic syndromes; S.A.: South Asia; TID: Tubulointerstitial diseases; USCA: United States-Canada-Australia.

found in the South Asia (Supplementary Figure 41). Unspecific PGN was most frequently found in the general age South Asians (47%, Supplementary Figure 42), which together with MPGN, it suggests South Asia as a main source of diagnosing PGN among NiS patients.

NiS-NS: NiS with nephrotic-range proteinuria

Three of the reviewed studies had discriminately reported their series with patients representing NiS-NS, and the epidemiology of their final diagnosis has been compared to that of the NiS-alone patients. As summarized in Table 2 and illustrated in the Supplementary Figures 43-50, NiS-NS patients represented higher diagnosis rates for MGN, FSGS, MPGN, MesPGN, and unspecific PGN than NiS-alone patients, while representing a lower frequency of IgA nephropathy. Lupus nephritis was comparably observed between the two groups.

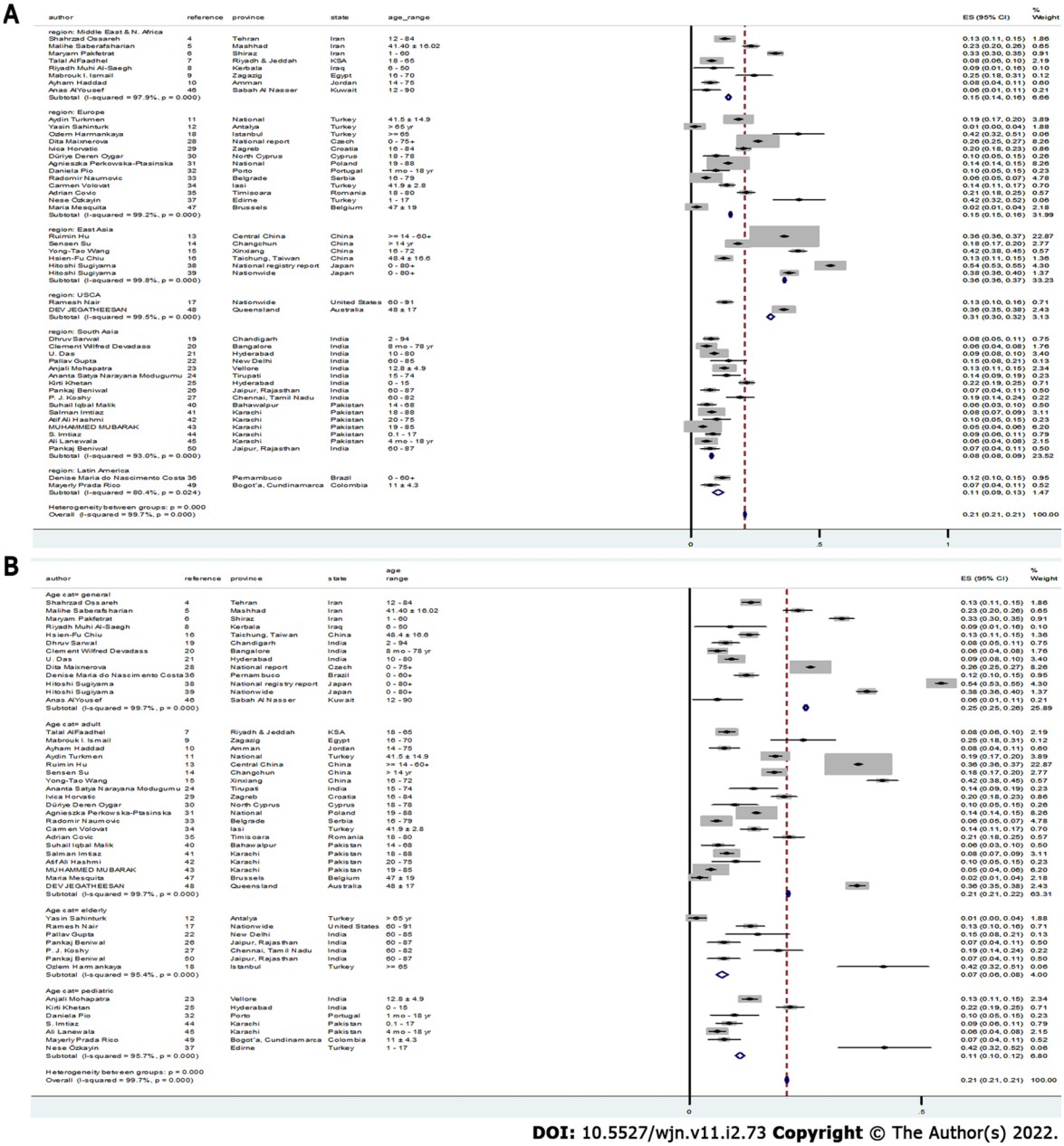

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Figure 2 Frequency of nephritic syndrome. A: Frequency of nephritic syndrome as indication for renal biopsy divided by the global region; B: Frequency of nephritic syndrome as indication for renal biopsy regarding the study subjects' age.

DISCUSSION

This study in all probability represents the literature with the single most comprehensive overview of NiS as the indication for renal biopsy procedure, the expected diagnoses, and predictive factors. The overall frequency of NiS as the indication for renal biopsies was about 21% of the total reports, with the highest rates in East Asia comprising over one third of all the cases (Japan represented the single highest frequency) and lowest in the South Asia (8%, Figure 2A). Patients of the general and adult age groups were the most likely age subgroups receiving kidney biopsies due to NiS, while pediatrics represented the lowest frequency of NiS as the indication for renal biopsies (Figure 2B).

Compared to the other renal syndromes, this study showed that NiS is associated with significant bias in the frequency of different final diagnoses. Some of the renal diagnoses (including proliferative endocapillary glomerulonephritis, hepatitis B virus nephropathy, IgM nephropathy, and minor glomerular abnormalities) were in such scarcity in NiS patients that this led to their exclusion from the final report, while some of which were quite frequent diagnoses in patients with other renal syndromes [2,3,50]. MGN was a dominant diagnosis in nephrotic syndrome patients comprising about 20% of the total population[2], however, this rates in the sub-nephrotic proteinuria[3] and NiS (current report), were much lower (7.5% and 6%, respectively). On the other hand, IgA nephropathy was the most likely diagnosis in NiS patients comprising over one third of all the diagnoses, while these rates for the sub-

nephrotic proteinuria and nephrotic syndrome were much less (17% and 4.5%, respectively)[2,3].

The global disparities in the epidemiology of the final diagnoses being made on renal biopsies of patients representing with any renal syndrome is also of extreme interest. For example, a previous systematic review has demonstrated that IgA nephropathy is most prevalent in the East Asia, comprising more than one third of all the diagnoses made for patients undergoing renal biopsies for any indication. However, this will be of limited practical relevance due to the profound disparity in diagnoses expected for different renal syndromes. For instance, the incidence of IgA nephropathy in the East Asia as reported by the current study was roughly 50% for NiS patients, far more than its overall frequency reported for the same region when estimated irrespective of the clinical syndrome (approximately 35%); similar observations have been made for nephrotic syndrome and sub-nephrotic proteinuria in the previous systematic reviews[2,3].

The next region representing a highly skewed frequency for a specific diagnosis was Latin America for lupus nephritis (approximately 44%); interestingly, considering the same concept for nephrotic syndrome and sub-nephrotic proteinuria, Sub-Saharan Africa and the Middle East were, respectively, the predominant regions of high frequency (approximately 12% and approximately 14%), with the former having no representative patients in the current review study on NiS.

A profound discrepancy has also been detected in the frequency of renal diagnoses regarding the reports' age groups. While MCD, lupus nephritis, hereditary nephropathy, MesPGN, and unspecific PGN made the predominant diagnoses in the pediatric NiS patients, about 43% of adults were finally diagnosed with IgA nephropathy. A similar observation was observed for the elderly population with over 45% of them being diagnosed with crescentric nephropathy. Predictably, the elderly population was the predominant age subgroup for the diagnosis of vascular nephropathies (including NAS), TID, diabetic nephropathy, and PPEs. Here again, a profound bias has been detected in the epidemiology of renal diagnoses regarding the clinical syndromes. For example, for nephrotic syndrome[2], about half of the pediatric patients were ultimately diagnosed with MCD, while this percentage was about 8% for sub-nephrotic proteinuria[3], and 6% for NiS patients (current study). Detection of MCD such a high percentage of pediatric patients with NiS is a considerable finding and changes presumptions. The next substantial disparity was detected for MGN in the elderly, with 35%, approximately 19% and 2.3% rates of diagnosis, respectively, for nephrotic, sub-nephrotic, and NiS (2, 3 and current study).

Meta-analyses from the current study have also revealed age-dependent disparities in the frequencies of final diagnoses. For example, the frequency of IgA nephropathy in NiS patients was by far highest among adults, while in the contexts of nephrotic syndrome or sub-nephritic proteinuria, pediatric patients were the age subclass most likely to be diagnosed with the entity, with a decreasing trend being detected with increases in the age subclasses (lower for adults and then the lowest in the elderly)[2,3].

Subcategorization of the reports simultaneously for their age and the global regions also revealed some very interesting and unprecedented observations. Two of the most interesting findings were the high rates of diagnosing crescentric nephropathy in various age subclasses from regions with the majority white ethnicity (Europe, United States, and Australia), as well as South Asia being the leading source of MPGN diagnosis in all their age subgroups; both the abovementioned suggest high levels of ethnic liability, environmental predispositions, and life-style effects on the epidemiology of renal diseases even within the same clinical syndromes.

Another subject of analysis in this study was the NiS-NS subgroup whose clinical syndrome included NiS with nephrotic range proteinuria that had been reported in a subgroup of patient populations by some of the reviewed studies. A comparison of NiS-NS epidemiological findings with the respective results from subnephrotic proteinuria, NiS-(alone) and nephrotic syndromes suggests that NiS-NS patients exhibit considerable disparities in the frequencies of renal diagnoses, proposing NiS-NS as a new syndrome entity. Although the limited sample size, as well as the disparities in other potential intervening factors, could confound the conclusion.

The findings of the current study are associated with limitations. The limited number of reports from specific regions of the world, the small sample sizes for each study and occasionally selection deviations in some of the studies (*e.g.*, age specific reports) were the most important limitations. For example, a finding of this study was the preponderance of crescentric nephropathy as the final diagnosis of NiS patients for both the elderly patients among the age subgroups and United States-Australia regarding the regional analyses. Together, it is conceivable that the observed high frequency of crescentric nephropathy diagnosis reported for the latter might in part be due to the potential inclusion of relatively older patients compared to the reports from the other global regions. Finally, sub-Saharan Africa had no representative in this review, and therefore the results of this study might not be well applied to patients from this region/ethnicity.

CONCLUSION

In conclusion, NiS, as the indication for renal biopsy, represents a very distinctive epidemiology of renal diagnoses than those of other major syndromes. Within the NiS group, there is a wide spectrum of epidemiological variations regarding the age subclasses as well as the regions of studies. Understanding

of these disparities helps the researchers, clinicians, and the health care systems in the management of their patients, and helps societies plan the best way to assign available resources to the areas that might promise more health advantages. It also provides motivations for future research to find the reasons behind the reported disparities and to intervene accordingly.

ARTICLE HIGHLIGHTS

Research background

Nephritic syndrome (NiS) is a major indicator of severe kidney disease requiring renal biopsy for histopathological evaluation, but limited understanding of the syndrome and its significance is currently lacking due to the lack of a comprehensive review in the literature.

Research motivation

The current understanding on the epidemiology of renal diseases finally diagnosed in patients representing various clinical syndromes as indications for the renal biopsy is inaccurate and skewed.

Research objectives

This systematic review aims at collecting the available data in the literature to give the most possible comprehensive overview on the epidemiology of diagnoses that we may expect from the evaluations of renal biopsies in patients with nephritic syndrome.

Research methods

A systematic review of the literature has been conducted, with 47 studies identified for meta-analyses.

Research results

A myriad of results have been made through this systematic review, the most important of them is the high prevalence of immunoglobulin A nephropathy (about 38%) as the final diagnosis of nephritic syndrome, and diagnosing minimal change disease in a proportion of pediatric patients representing with NiS.

Research conclusions

The diagnostic spectrum of nephritic syndrome is quite wide, and clinicians should have a better overview on all the possibilities.

Research perspectives

It has clinical, research and health care perspectives to the society.

FOOTNOTES

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Country/Territory of origin: Iran

ORCID number: Saeed Taheri 0000-0003-3034-0674.

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Editorial Board Member of *World Journal of Nephrology*, Ernesto Sabath, MD, PhD, Assistant Professor, Chief, Department of Nephrology, Hospital General de Querétaro, Nutrition School, Faculty of Natural Sciences, Universidad Autónoma de Querétaro, Fray Luis de Leon 1990, Queretaro 76000, México. esabath@yahoo.com

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The primary aim of *World Journal of Nephrology* (*WJN*, *World J Nephrol*) is to provide scholars and readers from various fields of nephrology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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MINIREVIEWS

Reno protective role of amlodipine in patients with hypertensive chronic kidney disease

Georgi Abraham, A Almeida, Kumar Gaurav, Mohammed Yunus Khan, Usha Rani Patted, Maithrayie Kumaresan

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Georgi Abraham, Department of Nephrology, MGM Healthcare, Nelson Manickam Road, Aminjikarai, Chennai 6300028, India

A Almeida, PD Hinduja Hospital and Medical Research Center, Almeida, A (reprint author), PD Hinduja, Hinduja Clin, Dept Med, Nephrol Sect, 2209 Veer Savarkar Marg, Bombay 400016, Maharashtra, Mumbai 400016, India

Kumar Gaurav, Mohammed Yunus Khan, Usha Rani Patted, Medical Affairs, Dr. Reddys Labs, Hyderabad 500016, Telangana, India

Maithrayie Kumaresan, Medical Affairs, Madras Medial Mission Hospital, Chennai 600037, India

Corresponding author: Mohammed Yunus Khan, MD, Medical Affairs, Dr. Reddys Labs, 7-1, 27, Ameerpet Road, Leelanagar, Ameerpet, Hyderabad 500016, Telangana, India.
doctorkhan26@gmail.com

Abstract

Chronic kidney disease (CKD) and hypertension (HTN) are closely associated with an overlapping and intermingled cause and effect relationship. Decline in renal functions are usually associated with a rise in blood pressure (BP), and prolonged elevations in BP hasten the progression of kidney function decline. Regulation of HTN by normalizing the BP in an individual, thereby slowing the progression of kidney disease and reducing the risk of cardiovascular disease, can be effectively achieved by the anti-hypertensive use of calcium channel blockers (CCBs). Use of dihydropyridine CCBs such as amlodipine (ALM) in patients with CKD is an attractive option not only for controlling BP but also for safely improving patient outcomes. Vast clinical experiences with its use as mono-therapy and/or in combination with other anti-hypertensives in varied conditions have demonstrated its superior qualities in effectively managing HTN in patients with CKD with minimal adverse effects. In comparison to other counterparts, ALM displays robust reduction in risk of cardiovascular endpoints, particularly stroke, and in patients with renal impairment. ALM with its longer half-life displays effective BP control over 24-h, thereby reducing the progression of end-stage-renal disease. In conclusion, compared to other classes of CCBs, ALM is an attractive choice for effectively managing HTN in CKD patients and improving the overall quality of life.

Key Words: Amlodipine; Chronic kidney disease; Hypertension; End-stage-renal disease; Monotherapy; Combination therapy

Core Tip: Amlodipine (ALM) is a powerful, well-tolerated, and safe anti-hypertensive agent widely used alone or as a key component of combination therapy for hypertension in chronic kidney disease (CKD). Its effectiveness in reducing blood pressure has proven benefits in cardiovascular event reduction and progression of renal disease. Overall, ALM emerges as the drug of choice in comparison to the newer calcium channel blockers in terms of its effectiveness and potency in BP lowering in CKD patients.

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INTRODUCTION

Hypertension (HTN) – also known as high blood pressure (BP) – is a significant medical illness in which the arterial BP remains consistently high, with a systolic BP (SBP) of 140 mmHg or higher or a diastolic BP (DBP) of 90 mmHg or higher[1]. The World Health Organization has identified HTN as one of the most important risk factors for morbidity and mortality worldwide, with roughly 9 million people dying each year[2]. Even though other risk factors play a role, poor diets, such as excessive salt consumption, a diet high in saturated fat and trans-fats, low intake of fruits and vegetables, physical inactivity, tobacco/alcohol use, and being overweight/obese, appear to be the most common contributing factor to HTN. Non-modifiable risk factors include a family history of HTN, elderly age, and comorbidities such as diabetes or kidney disease[3]. According to recent analysis and observational research, people in Western countries have a higher prevalence of HTN and higher BP levels than those in other parts of the world, and this disparity is narrowing as non-Westerners adapt to Western culture and lifestyle[4].

HTN continues to be the greatest cause of premature mortality, affecting roughly 1.13 billion people globally and accounting for nearly 45% of deaths due to heart disease, 51% of deaths due to stroke, and 85%-95% of patients with chronic kidney disease (CKD)[5]. The overall prevalence of HTN in India was 29.8% from 1950 to 2014, according to data, and a meta-analysis of prior Indian prevalence studies showed a considerable increase in the incidence of HTN from the 1960s to the mid-1990s[6]. HTN prevalence studies in urban and rural populations from the mid-1990s to the present show a growing trend, with a bigger increase in urban (33.8%) than rural (27.6%) populations[6]. Early detection, consistent follow-up, and HTN control methods may be a cost-effective way to lower the worldwide disease burden associated with HTN.

HYPERTENSION AND CHRONIC KIDNEY DISEASE

CKD is characterized by persistent kidney damage, a decrease in the estimated glomerular filtration rate (eGFR), and the development of albuminuria. It is a long-term disorder that causes kidney function to deteriorate over time, eventually leading to kidney failure or end-stage renal disease (ESRD)[7]. CKD refers to all five stages of kidney damage, from very mild in stage 1 (eGFR ≥ 90 mL/min/1.73 m^2) to complete kidney failure in stage 5 (eGFR < 15 mL/min/1.73 m^2)[8] (shown in Table 1). In 2017, 12 million people died from CKD worldwide, with a global prevalence of 697.5 million. Women and girls had a greater age-standardized global prevalence of CKD (9.5%) than men and boys (7.3%), and China and India accounted for over one-third of all CKD cases (132.3 million and 115.1 million, respectively)[9]. Since the eGFR estimation equation and the Modification of Diet in Renal Disease formula have not been verified, the incidence of CKD in India is high[10]. The Indian Society of Nephrology established the Indian CKD Registry in 2005 as a comprehensive statewide data collection for examining all aspects of CKD. According to the initial research, diabetic nephropathy has emerged as the leading cause of CKD in India, according to a cross-sectional survey of 52273 adult patients[11].

HTN control is important in the care and well-being of CKD patients because it is both a cause and an effect of the disease, and it contributes to its progression[12]. Uncontrolled BP during the day causes a BP "load" in CKD patients, which is linked to eGFR decrease and proteinuria. Masked HTN, nocturnal

Table 1 Classification of chronic kidney disease Stages 1-5[8]

Stage	Description	GFR, mL/min/1.73 m^2
-	At increased risk	≥ 60
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney Failure	< 15 (or dialysis)

GFR: Glomerular filtration rate.

non-dipping, and 24-h day/night BP fluctuation are all seen in patients with CKD[12]. As evidenced by studies showing a higher risk of all-cause death, hemorrhagic strokes, and total cardiovascular (CV) events in people with CKD, BP fluctuation is a powerful predictor of end organ damage[13]. Furthermore, both HTN and CKD are independent risk factors for CVD, and when both are present, the risk of CVD morbidity and mortality is significantly enhanced. Furthermore, HTN has been recorded in 85%-95% of CKD (stages 3-5) patients[14]. The pathophysiology of HTN in CKD is multifaceted and complicated[15]. There is an upregulation of the renin–angiotensin–aldosterone system (RAAS) with a functional drop in eGFR, which increases salt and water retention even more, and this is compounded by an enhanced salt sensitivity of BP[16]. Proteinuria is a critical sign of renal impairment that is related with CKD progression and incident CVD in a gradual and independent manner. Reduced BP lowers proteinuria, which slows eGFR decline and lowers CV risk. When treating HTN in individuals with CKD, the influence of a medicine on proteinuria is a significant consideration in addition to its antihypertensive effects. Another emerging worry is the prevalence of treatment-resistant HTN in CKD, and including this patient population in large-scale randomized outcome trials may assist to guide future treatments[16].

BLOOD PRESSURE CONTROL IN CKD

Accurate and effective BP readings are required for optimal HTN therapy. Due to a lack of repeat measurements, diurnal variation in BP, and white-coat HTN, BP obtained in clinic or office BP recordings may provide an erroneous assessment of the clinical condition[17,18]. Different phenotypes of HTN have been identified and linked to varying degrees of CVD risk and all-cause death(shown in Table 2). In comparison to clinic measurements, 24-h ambulatory BP monitoring is more reliable, since it allows assessment of diurnal fluctuation in BP and serves as a stronger predictor of CVD events in people with CKD, according to the 2017 American College of Cardiology guidelines[19]. Home BP monitoring is a less resource-intensive alternative technique, and individuals who acquire data from home readings have better overall BP control than those who do not. HTN and CKD have a cause-and-effect connection that is intertwined. A rise in BP is linked to a reduction in kidney function, and a continuing rise in BP is linked to a faster development of renal function decline. As people get older, the prevalence of HTN rises, making BP control more challenging[20]. As a result, HTN control is an important part of CKD patient treatment, and medicines that provide 24-h BP control and thus minimize BP variability should be the preferred therapeutic option for CKD patients.

USE OF ANTI-HYPERTENSIVE AGENTS IN CKD

HTN management in CKD is critical for patients because HTN treatment can improve CV outcomes in patients with ESRD and CKD[20]. The treatment of HTN is crucial in the management of CKD. HTN is common in people with CKD and ESRD because it is both a cause and a consequence of the disease. In addition, HTN therapy is linked to better CV outcomes in both CKD and ESRD patients. As a result, both the patient and the practitioner must be vigilant when dealing with HTN in CKD[20]. Dietary salt restriction, maintaining an adequate dry weight, and lifestyle changes are among nonpharmacological therapies for HTN. These techniques, however, are ineffective in treating HTN and must be combined with pharmacological therapies for more efficient BP control in the CKD population[16].

Several anti-hypertensive drug types may be useful in the treatment of CKD with HTN[21]. Most patients with CKD and HTN should start with BP medications that also reduce proteinuria. Proteinuria reduction results in long-term improvements in both CV and renal outcomes, according to data[16].

Table 2 Association of hypertension phenotype with all-cause mortality[18]

BP phenotype	Description[1]	All-cause mortality hazard ratio (95%CI)
Normotension	Normal clinic BP, normal 24-h ABPM	Reference
White-coat hypertension	High clinic BP, normal 24-h ABPM	1.79 (1.38–2.32)
Sustained hypertension	High clinic BP, high 24-h ABPM	1.80 (1.41–2.31)
Masked hypertension	Normal clinic BP, high 24-h ABPM	2.83 (2.12–3.79)

[1]Normal clinic BP defined as < 140/90 mmHg, Normal 24-h BP defined as < 130/80 mmHg. Values represent patients on treatment and without chronic kidney disease. ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; CI: Confidence interval.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which target the RAAS, are commonly used as first-line antihypertensive medications[22]. However, it is widely known that RAAS inhibitors cause hyperkalemia, and that when an ACE and an ARB inhibitor are coupled, renal function is worsened and hypotension occurs[22]. Hyperkalemia was found to be common in patients with CKD who were treated with RAAS inhibitors, and as a result, RAAS inhibitors should be used with caution in patients with underlying CKD and HTN[23]. A preferable first-line therapy in patients without proteinuria has not been firmly established, and drugs such as thiazides may be tried.

Patients with CKD and HTN frequently develop fluid retention/fluid overload, necessitating the use of diuretics in their treatment plan[24]. Thiazides are suggested for people with CKD stages 1 to 3 (GFR 30 mL/min) and have been shown to be beneficial in lowering BP and reducing the risk of CVD. In addition, loop diuretics are favored in patients with CKD stage 4 or 5 (GFR 30 mL/min) because they have been found to be more successful in lowering extracellular fluid volume in individuals with significantly reduced GFR[12,20]. Beta-blockers have a limited effect on CKD progression and proteinuria, thus they are only used as a second- or third-line treatment if the patient has a compelling reason to take one, such as coronary artery disease or chronic heart failure[25]. When first- and second-line therapy fails to reach BP targets, aldosterone receptor antagonists such as spironolactone and eplerenone may be used in CKD treatment[21]. When used with an ACE inhibitor or an ARB, these drugs reduce proteinuria. Aliskiren, a renin inhibitor, is the only drug approved for the treatment of HTN as a monotherapy or in combination with valsartan[26]. Because of the increased risk of renal impairment, hypotension, and hyperkalemia, the ALTITUDE trial has led to the contraindication of its usage with ACE/ARB inhibitors in patients with diabetes or renal impairment[27]. If a patient is unable to take an ACE inhibitor or an ARB, Aliskiren may be tried; however, it is not indicated for individuals with stage 4 or 5 renal failure.

Calcium channel blockers (CCBs) are drugs that relax blood arteries and enhance blood and oxygen supply to the heart while lowering the strain of the heart[28]. Based on electrophysiological and pharmacological features, CCBs are classified as L-, N-, P-, Q-, R-, and T-type[29]. L-type voltage-gated CCBs are potent vasodilators that are commonly utilized as first- or second-line treatments for HTN. In the treatment of HTN in patients with CKD, they are considered second- or third-line therapy[30]. Dihydropyridines (DP) and non-NDP are two types of CCBs that have been demonstrated to be effective in the treatment of HTN in patients with CKD[31]. In non-proteinuric CKD, DP CCBs [such as amlodipine (ALM), cilnidipine, felodipine, nifedipine, and others] can be utilized as first-line therapy alone or in combination, but their impact in proteinuric CKD is inferior to RAAS inhibition[32]. Adding DP CCB to proteinuric patients with RAAS inhibition improves BP control without worsening proteinuria, according to European Society of Hypertension/European Society of Cardiology guidelines, which recommend combination therapy with an ACE inhibitor and CCB as first-line therapy in proteinuric circumstances[33]. In conclusion, the decision to use one medication over another is based on patient-specific considerations such as probable adverse effects, cost, and other underlying comorbidities.

EMERGENT ROLE OF CCBS IN PATIENTS WITH HTN AND CKD

The most potent and common situation presently is the use of CCBs and RAAS inhibitors (ACE/ARB) as anti-hypertensive medicines for mild to moderate HTN. Although there is no consensus on which antihypertensive drugs should be given as first-line therapy in patients with CKD, a systematic review and meta-analysis of 21 randomized controlled trials (RCTs) involving 9492 patients found that CCBs and RAAS inhibitors had similar BP-lowering effects in HTN patients with CKD and ESRD[34]. In the test population, there were no significant changes in long-term BP maintenance, mortality, heart failure, stroke, cerebrovascular episodes, or renal function. Overall, this study demonstrated that CCBs are comparable to RAAS inhibitors and can protect the kidneys in CKD patients with HTN. This was in line

with a prior study (ALLHAT) that found CCBs to be particularly beneficial for long-term GFR maintenance when compared to diuretics and ACE inhibitors[35]. Furthermore, the INSIGHT study randomized 6321 HTN patients with one or more related risk factors to the DP CCB, nifedipine gastrointestinal therapeutic system, or the diuretic combination hydrochloro-thiazide amilozide for the treatment of HTN. The major composite end point of CV mortality, non-fatal myocardial infarction, stroke, and heart failure had no statistically significant difference in both groups throughout the trial [36]. The ACCOMPLISH (Avoiding CV Events *via* Combination Therapy in Patients Living with Systolic Hypertension) trial compared the effectiveness of ALM/ACE inhibitor against hydrochloro-thiazide/ACE inhibitor combination therapy in adults with HTN and CKD in lowering CVD mortality [37]. The superior efficacy of ALM plus ACE inhibitor on CVD mortality was revealed in this multicenter, double-blind, randomized experiment. Notably, the ALM group had a considerably decreased probability of CKD progression, which was independent of BP values obtained. In the HTN/CKD group, the addition of ALM to ACE inhibitor therapy appears to provide an additional Reno protective benefit compared to the addition of a thiazide diuretic. In summary, the anti-hypertensive use of CCBs in patients with CKD is an attractive option for reducing BP variability with minimal side effects.

In certain countries, DP CCBs are a common class of antihypertensive medicines. ALM and barnidipine, for example, are third generation DPs that are more lipophilic and have stable pharma-cokinetics with long-term effects. They are well tolerated in people with heart failure and advantageous for those with CKD since they are less cardio-selective[31].

AMLODIPINE-THE UNIQUE CCB

DP CCBs are a class of potent, well-tolerated, and safe medicines that are widely used to treat high BP as a monotherapy or as a crucial component of HTN treatment[38]. ALM was first released in the early 1990s and has a number of distinguishing characteristics that set it distinct from other agents in this category. ALM is a longer-acting DP CCB that has been proven in trials to block all channels as well as the N-type channel more effectively than cilnidipine[39]. The elimination half-life of 40-60 h confers various pharmacokinetic properties not found with other calcium-antagonist medications due to its low clearance. It has a high oral bioavailability (60%-80%) and a steady-state accumulation with once-daily dosage over a period of 1-1.5 wk. Furthermore, the pharmacodynamic profile is consistent with the drug's disposition, with BP steadily decreasing over 4-8 h following a single dose and returning to baseline over 24-72 h. Furthermore, stopping ALM therapy causes a delayed restoration of BP to baseline over 7-10 d, with no indication of a 'rebound' impact.

It has great selectivity for vascular smooth muscle, limited impact on heart rate, no negative inotropic effects/electrophysiological disturbances, and milder side events[40]. It is a well-studied classic medication with a wide range of capabilities, including BP regulation and anti-anginal and anti-athero-sclerotic effects[41]. Studies documenting ALM's gradual and protracted drop in BP due to a long elimination half-life and delayed receptor dissociation kinetics[42,43] demonstrate its function in delaying the onset of CKD. ALM also has a long duration of action of at least 24 h and good anti-hypertensive effects with high safety in clinical trials with HTN patients at doses of 2.5-5 mg once a day [44]. Furthermore, 35 HTN patients with renal dysfunction were given ALM at 2.5-5.0 mg/d for 8 wk to examine its clinical efficacy and safety in HTN patients with renal dysfunction. With moderate side effects, target BP reduction was reached in 28 of the 35 patients (80%), and ALM was deemed clinically helpful in 27 of the 35 patients (77.1%)[45]. In a clinical trial, individuals treated with telmisartan and ALM combined therapy had a 70% lower urine albumin-to-creatinine ratio (UACR) than those treated with ALM alone[46]. In a similar vein, compared to high dose monotherapy of either medication alone, a low dose telmisartan–ALM combination showed considerably higher BP reductions for both SBP and DBP[47]. ALM safely lowers SBP in hypertensive hemodialysis patients and has a favorable influence on CV outcomes[48]. The link between ALM and contrast-induced acute kidney injury is uncertain, although a retrospective, matched cohort investigation in a large Chinese hypertension population found that ALM medication prior to contrast exposure protected hypertensive patients from contrast-induced acute kidney injury and increased survival[49]. Results from several trials proving the superiority of ALM in decreasing hypertensive CKD are shown below and summarized in Table 3.

ACCOMPLISH trial

This is a double-blinded, randomized trial with 11506 patients randomized benazepril (20 mg) and ALM (5 mg; n = 5744) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg; n = 5762), orally once a day, as previously stated in Section 4. In comparison to the hydrochlorothiazide plus benazepril, ALM plus benazepril group demonstrated a 48% reduction in the progression of CKD and 49% reduction in doubling of serum creatinine. Initiating antihypertensive treatment in CKD with benazepril plus ALM preference to benazepril plus hydrochlorothiazide should be preferred as it slows progression of nephropathy to a greater extent[37].

Table 3 Summarized data from various trials demonstrating the role of amlodipine in reducing hypertension

Trial	Objective	Design/primary endpoints	Drug/procedures used	Main outcomes	Benefits on renal parameters
ALLHAT	To determine whether treatment with a CCB or an ACE inhibitor lowers the incidence of CHD or other CVD events *vs* treatment with a diuretic	A total of 33357 participants aged 55 yr or older with HTN and at least 1 other CHD risk factor from 623 North American centers were enrolled. Primary Endpoints: Combined fatal CHD or nonfatal MI analyzed by intent-to-treat	Participants were randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n = 15 255); ALM, 2.5 to 10 mg/d (n = 9048); or lisinopril, 10 to 40 mg/d (n = 9054) for planned follow-up of approximately 4 to 8 yr	In patients with HTN, chlorthalidone, ALM, and lisinopril performed similarly in regard to fatal CAD and nonfatal MI	Post hoc analysis of the trial revealed that in hypertensive patients with reduced GFR, both ALM and lisinopril performed similarly in reducing the rate of development of ESRD
ACCOMPLISH	To evaluate the effect of ALM *vs* hydrochlorothiazide in patients with HTN who are at high risk CVD	Multi-centered, double-blind, randomized, controlled trial with 548 centers in the US and Europe. 11506 subjects were enrolled who received Benazepril/ALM (n = 5744) or Benazepril/HCTZ (n = 5762). Primary Endpoint: CV mortality, nonfatal MI, nonfatal CVA, UA, resuscitation after cardiac arrest, or coronary revascularization	Subjects received benazepril/ALM 20 mg/5 mg or benazepril/HCTZ 20 mg/12.5 mg daily. Benazepril component was increased to 40 mg after 1 mo.Increase of ALM to 10 mg or HCTZ to 25 mg to reach target BP < 140/90 or < 130/80	Among patients with HTN at high risk for CV complications, benazepril/ALM decreases the rate of CV events as compared to benazepril/HCTZ	Initial antihypertensive treatment with benazepril and ALM demonstrates a superior ability in reducing the progression of nephropathy
SAKURA	To clarify whether the L-/N-type CCB cilnidipine is more renoprotective than the L-type CCB ALM in patients with early-stage diabetic nephropathy	Prospective, multicenter, open-labeled, randomized trial in 77 clinics and hospitals in Japan, to probe the anti-albuminuric effects of cilnidipine and ALM in 367 RAAS inhibitor-treated patients with HTN (BP: 130-180/80-110 mmHg), type 2 diabetes, and microalbuminuria (UACR: 30-300 mg/g). Primary Endpoint: Change in the urinary albumin/Cr ratio after a 1-yr treatment	Study subjects were randomly allocated in two groups and treated with cilnidipine (started at 10 mg/d, then adjusted to 5-20 mg/d) or ALM (started at 5 mg/d, then adjusted to 2.5-10 mg/d). The target BP was < 130/80 mm Hg	Cilnidipine did not offer greater renoprotection than ALM in RAS inhibitor treated HTN patients with type 2 diabetes and microalbuminuria	In hypertensive patients with proteinuria, L/N- and L/T-type CCBs as add-on therapy to an ACEI or an ARB reduce albuminuria and proteinuria and improve kidney function compared with the use of an ACEI or ARB alone or in combination with other antihypertensive agents
ASCOT-BPLA	To evaluate whether treatment with a newer anti-hypertensive regimen of CCB with or without an ACE inhibitor is more effective than an older regimen of β-blocker with or without a diuretic, and whether it reduces CHD events in hypertensive patients with relatively low cholesterol levels	A total of 19257 patients with SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg (untreated) or SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg (treated); total cholesterol ≤ 6.5 mmol/L (250 mg/dL) and triglycerides ≤ 4.5 mmol/L (400 mg/dL); age 40-79 yr; ≥ 3 CVD risk factors; and no history of CHD were enrolled Primary Endpoints: Nonfatal MI and fatal CHD	Patients were randomized open-label to one of the two anti-hypertensive treatments: ALM 5 mg (n = 9639) or atenolol 50 mg (n = 9618). In order to achieve target BP goals of < 140/90 mm Hg, study drug doses were increased, and second-line drugs were added (perindopril 4 mg for the ALM group and bendroflumethiazide 1.25 mg for the atenolol group)	ALM-based regimen is superior to an atenolol-based regimen in regard to demonstrating a greater reduction in BP variability and prevention of major CV events in patients with HTN	ALM based arm demonstrated a significant reduction in new onset diabetes mellitus, development of peripheral arterial disease and renal impairment

ACEI: Ace inhibitor; ALM: Amlodipine; ARB: Angiotensin receptor blockers; BP: Blood pressure; CAD: Coronary artery disease; CCB: Calcium channel blocker; CHD: Chronic heart disease; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; GFR: Glomerular filtration rate; HCTZ: Hydrochlorothiazide; HTN: Hypertension; MI: Myocardial infarction; SBP: Systolic blood pressure; RAAS: Renin–angiotensin–aldosterone system; UACR: Urine albumin-to-creatinine ratio.

SAKURA trial

The Study of Assessment for Kidney Function by Urinary Microalbumin in Randomized (SAKURA) experiment was conducted to examine the anti-albuminuric effects of L-/N-type and L-type CCBs in HTN patients with diabetes and microalbuminuria. The anti-albuminuric effects of cilnidipine and ALM were investigated in RAAS inhibitor-treated patients with HTN (BP: 130-180/80-110 mmHg), type 2 diabetes, and microalbuminuria (UACR: 30-300 mg/g) in this prospective, multicenter, open-labeled, randomized investigation. Despite the fact that cilnidipine and ALM both reduced BP and showed

similar effects on UACR, ALM provided greater renoprotection in RAS inhibitor-treated hypertensive patients with type 2 diabetes and microalbuminuria. Clinidipine provided no more renoprotection than ALM in RAS inhibitor-treated hypertensive patients with type 2 diabetes and microalbuminuria.

ASCOT-BPLA trial

The Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm (ASCOT-BPLA) trial found that an ALM-based regimen outperformed an atenolol-based regimen in terms of lowering BP variability and preventing major CV events in patients with HTN[51].

Treatment-resistant HTN is emerging as an increasingly recognized problem and is markedly over-represented in patients with CKD[52]. It is defined as uncontrolled BP despite maximally effective dosing of three drugs from different classes, one of which should be a diuretic. Recent evidence has highlighted the heightened risk for both adverse renal and CV outcomes associated with resistant HTN, even when BP control is attained[52]. In a study involving 157 resistant HTN patients (over 60-years-old) who were randomized to 8 wk of treatment and received double-blinded treatment with placebo, ALM (10 mg/d), olmesartan medoxomil (40 mg/d), and ALM (10 mg/d) + olmesartan medoxomil (40 mg/d), the research findings suggested that ALM and OM combination therapy had superior efficacy to ALM or OM monotherapy, Furthermore, patients who received combination therapy met their BP goals more often than those who received placebo, ALM, or OM monotherapies. The long-term CV effects of ALM were compared to other classes of anti-hypertensive medicines in high-risk HTN patient subgroups with diabetes and/or renal failure in another investigation[53]. Thirty-eight RCTs comparing ALM/CCBs to diuretics, -blockers, ACE/ARB inhibitors, and -blockers with a 6-mo follow-up were enrolled, with BP and CV events examined. ALM was found to be successful in lowering SBP and DBP, making it a promising treatment alternative for the long-term management of HTN in diabetic and renal failure patients. In terms of preventing major CV events and causing less diabetes, an ALM-based regimen was found to be superior than an atenolol-based regimen[54].

CONCLUSION

CCBs are a good choice of anti-hypertensive medications in HTN patients with CKD. ALM is a well-known medication having a wide range of effects, including BP regulation and anti-anginal and anti-atherosclerotic characteristics. ALM is a longer-acting DP CCB that controls BP for up to 24 h and minimizes BP variability. Several pharmacokinetic properties can be linked to it, including limited clearance and a longer rate of elimination (elimination half-life of 40-60 h). It also has a high oral bioavailability and a steady-state accumulation with once-daily treatment. In the absence of albuminuria and with a preserved GFR (> 60 mL/min), it can be used as a first-step therapy since it can block all calcium channels and the N-type channel more effectively than cilnidipine. It is a strong, well-tolerated, and safe antihypertensive drug that is commonly used for HTN in CKD, either alone or as part of a combination therapy. Its effectiveness in lowering BP has been linked to a reduction in CV events, as evidenced by large RCTs. ALM in combination with other medicines that elicit RAAS blockage (ACE/ARB) has been demonstrated to be an effective BP-lowering strategy in reducing CV risk and slowing the progression of renal impairment. AML substantially lowers BP in patients with HTN and renal impairment while causing minimal or little worsening of renal dysfunction. In terms of effectiveness and potency in decreasing BP in CKD patients, ALM emerges as the medicine of choice when compared to the newer CCBs.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Georgi Abraham 0000-0002-6957-2432; A Almeida 0000-0003-2016-7273; Kumar Gaurav 0000-0002-1201-

5280; Mohammed Yunus Khan 0000-0002-9402-9909; Usha Rani Patted 0000-0002-4815-3300; Maithrayie Kumaresan 0000-0001-6554-5712.

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MINIREVIEWS

Liposoluble vitamins A and E in kidney disease

Maria Helena Rojo-Trejo, Ma Ludivina Robles-Osorio, Ernesto Sabath

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Maria Helena Rojo-Trejo, Ma Ludivina Robles-Osorio, Nutrition School, Universidad Autónoma de Querétaro, Querétaro 76910, Mexico

Ernesto Sabath, Department of Renal Medicine, Nutrition School, Universidad Autónoma de Querétaro, Querétaro 76090, Mexico

Corresponding author: Ernesto Sabath, MD, PhD, Assistant Professor, Director, Department of Renal Medicine, Nutrition School, Universidad Autónoma de Querétaro, Fray Luis de León 1990, Querétaro 76090, Mexico. esabath@yahoo.com

Abstract

Kidney disease (KD) is characterized by the presence of elevated oxidative stress, and this is postulated as contributing to the high cardiovascular morbidity and mortality in these individuals. Chronic KD (CKD) is related to high grade inflammatory condition and pro-oxidative state that aggravates the progression of the disease by damaging primary podocytes. Liposoluble vitamins (vitamin A and E) are potent dietary antioxidants that have also anti-inflammatory and antiapoptotic functions. Vitamin deficits in CKD patients are a common issue, and multiple causes are related to them: Anorexia, dietary restrictions, food cooking methods, dialysis losses, gastrointestinal malabsorption, *etc.* The potential benefit of retinoic acid (RA) and α-tocopherol have been described in animal models and in some human clinical trials. This review provides an overview of RA and α tocopherol in KD.

Key Words: Retinoic acid; α-Tocopherol; Oxidative stress; Kidney disease; Podocyte; Cardiovascular disease

Core Tip: Oxidative stress in patients with kidney disease (KD) is an important risk factor for cardiovascular disease. Vitamin A and E are important antioxidants with many roles in health and KD. High levels of vitamin A may have adverse health effects but higher levels of vitamin E have been associated with a lower overall mortality. Exogenous administration of these vitamins to patients with KD have shown controversial results.

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INTRODUCTION

Kidney disease (KD) is characterized by the presence of elevated oxidative stress and this is postulated to contributing to the high cardiovascular mortality in these individuals. Liposoluble vitamins (vitamins A and E) are potent dietary antioxidants that also have anti-inflammatory and antiapoptotic functions. Antioxidant therapies have been extensively used to decrease oxidative stress and cardiovascular disease (CVD) risk. In the kidneys, the beneficial effects of retinoic acid (RA) have been reported in multiple disease models, such as glomerulosclerosis, renal fibrosis, and acute kidney injury (AKI).

Vitamin E has a myriad of cellular effects, such as decreasing the synthesis of pro-inflammatory molecules and oxidative stress response, inhibiting the nuclear factor-kappaB (NF-kB) pathway, regulating cell cycle, and inhibiting the expression of pro-apoptotic factors that can have a positive impact on KD. The aim of this review is to present an overview about the impact of liposoluble vitamins on KD.

Vitamin A metabolism

Vitamin A, is the name of a group of fat-soluble retinoids, including retinol and retinyl-esters that are essential for human survival; vitamin A is available into the human diet by intake of either food containing preformed vitamin A (*e.g.*, red meats) or carotenoids (*e.g.*, carrots and green leafy vegetables).

Retinoids are vital for human health and play a crucial role in the regulation of nocturnal vision, reproduction, immune function, and cell differentiation[1,2]. Recent advances in the study of retinoids metabolism have highlighted their importance in adipose tissue biology, glucose metabolism, and bone mineralization[3,4].

Most actions of retinol are mediated by its metabolite all-trans (AT)RA, which is synthesized intracellularly in target tissues from retinol[5]. Retinol is stored primarily as retinyl ester in the hepatic stellate cells, and to a lesser extent, in adipose tissue and other extrahepatic sites.

Retinoids regulate a number of physiological processes and through regulating the expression of over 500 genes; retinoids bind to nuclear receptors called RA receptors and retinoid X receptors, which themselves are DNA-binding transcriptional regulators and members of the nuclear hormone receptor family[6].

The liver plays a central role in vitamin A physiology. The retinol-binding protein 4 (RBP4) is secreted from the liver to bind and transport vitamin A to extrahepatic target tissues for intracellular ATRA synthesis. The primary physiological role of RBP4 is to guarantee a constant and continuous supply of retinol to peripheral tissues despite fluctuations in dietary vitamin A intake[7,8].

Vitamin A homeostasis in kidney health and disease

The kidney plays a key role in vitamin A homeostasis; findings of kinetic studies have revealed that approximately 50% of the circulating retinol pool originates in the kidneys. Retinol is filtered through the glomerular barrier and is then taken up in the proximal tubule by the endocytic receptor megalin; kidney-specific megalin deletion in mice, increases the urinary excretion of retinol and RBP4; in these mice, the syntheses of hepatic retinol and retinyl esters is reduced. These findings suggests a more complex role of the kidney in retinoid homeostasis[9]. More than 99% of retinol is reabsorbed by the proximal renal tubule; RBP4 has been identified as a very sensitive biomarker for proximal tubular cells dysfunction[10].

Patients with impaired renal function have been reported to have high circulating levels of retinol and RBP4, possibly due to a combination of decreased retinol-RBP4 complex clearance, reduced conversion of retinol to ATRA, and tissue accumulation of RBP4[11]. Dialysis patients have elevated serum levels of retinol and RBP4[12].

Increased RBP4 concentrations has been associated with an increased risk for osteoporosis, heart disease, and dyslipidemia. Furthermore, many studies have demonstrated an important link of RBP4 with adiposity, insulin resistance, and type II diabetes[4,13,14]. Interestingly, ATRA has been shown to be inversely associated with CVD and mortality in dialysis patients[12].

Dietary intake of vitamin A in chronic KD

The most important food sources of vitamin A are liver, fish liver oil, dairy products (butter, milk, *etc.*), egg yolk, dark green leafy vegetables, and deeply colored yellow/orange vegetables and fruits[15]. The recommended dietary allowance for men and women is 900 and 700 μg retinol activity equivalents/d,

respectively[16].

The Kidney Disease Outcomes Quality Initiative guideline no recommends routinely vitamin A supplementation (grade opinion), and there are no studies about the nutritional requirements in chronic KD (CKD) population[17]. There is no information about dietary recommendations in the pediatric population with CKD.

There are only a few studies that have evaluated vitamin A intake in CKD and dialysis subjects. In a cross-sectional study of 91 hemodialysis patients, only 23% of individuals covered vitamin A dietary recommendation[18]. As most sources of vitamin A have high potassium and phosphorous contents, the intake of vitamin A may be limited in advanced stages of CKD. Cooking techniques used to lower potassium in foods affect carotene concentration; boiling decreases up to 20%-30% of carotene content after 30 min, thereby making it more difficult to achieve adequate vitamin intake[19].

Kidney development and vitamin A

Vitamin A and its metabolites have a pivotal role during prenatal development, and vitamin A status is critical for the fetus. Maternal vitamin A deficiency is associated with preterm delivery, fetal death, or major congenital malformations in the offspring[20]. Studies in rodents suggest that retinol availability is essential in order to have an adequate renal development. Fetal retinol crosses the placental barrier from the maternal circulation and is converted to ATRA in peripheral tissues. Vitamin A deficiency has been associated in pregnant rats with mild renal hypoplasia in term fetuses; and the addition of ATRA to fetal rat kidneys cultured *ex vivo* accelerates new nephron formation[21-23].

The expression of the proto-oncogene c-ret, which plays an essential role in renal organogenesis, is modulated by retinoid environment. This indicates that the control of nephron mass by vitamin A may partly be mediated by the tyrosine kinase receptor ret, and this receptor modulates the ureteric bud branching morphogenesis[21].

In a cohort of 9-13 years old children in Nepal whose mothers participated in a randomized controlled trial of vitamin A supplementation before, during, and after pregnancy, the rate of hypertension or microalbuminuria did not differ by supplement group[24]. In conclusion, adequate vitamin A supply is crucial in determining final nephron numbers, and whether these findings have a prime role in the further development of CKD or hypertension is still controversial[25].

Glomerular barrier and retinoids

The glomerular filtration barrier consists of three layers: Fenestrated endothelial cells, glomerular basement membrane, and podocytes. Podocytes are specialized epithelial cells, whose major function is regulation of the glomerular filtration. Podocyte injury is implicated in many glomerular diseases including focal segmental glomerular sclerosis, diabetic KD, and human immunodeficiency virus (HIV)-associated nephropathy; loss of podocytes contributes to progressive KD as these cells have a low proliferative capacity. Research on podocytes and retinoids has been the subject of recent excellent reviews [26,27]. The pleiotropic effects of retinoids in animal models of KD are shown in Table 1. In HIV-1-transgenic mice, ATRA inhibits proliferation and induces differentiation in podocytes through cAMP/PKA activation[28].

Retinoid treatment of rats with experimental mesangioproliferative glomerulonephritis causes a significant reduction in albuminuria, inflammation, and cell proliferation. Retinoids have been demonstrated to induce a marked reduction in renal transforming growth factor (TGF)-β1 and TGF receptor II expression[29]. NF-κB and nitric oxide synthase expression are reduced in mesangial cells after ATRA administration[30]. Renin-angiotensin system activity is also reduced[31]. Retinoids restore injured podocytes that regulate the transition of parietal epithelial cells to podocytes in rat models of glomerular inflammation (Figure 1)[32].

There are some reports of conspicuous clinical improvement in patients with lupus nephritis by using retinoid treatment[33]. In models of diabetic nephropathy, ATRA suppressed inflammatory changes and decreased proteinuria[34], and ATRA is significantly decreased in the cortex, which indicates that ATRA metabolism is markedly dysregulated in diabetic kidneys[35]. In Table 1 some postulated mechanisms of action of retinoid administration in animal models of KD and reported human clinical trials are described.

ATRA and AKI

ATRA has been used therapeutically to reduce injury and fibrosis in models of AKI. ATRA signaling is activated in tubular epithelial cells and macrophages and reduces macrophage-dependent injury and fibrosis after AKI[36]. In models of cisplatin and contrast-induced AKI, retinoids activate autophagy, inhibit apoptosis, and decrease the oxidative status[37].

Retinoids and erythropoietin in kidney failure

Erythropoietin (EPO) synthesis decreases in kidney failure, and some of the mechanisms proposed are the conversion of peritubular fibroblast into α-smooth muscle actin-expressing myofibroblasts, thereby losing their ability to secrete retinoids and EPO and defects in oxygen sensing[38]. Liver cells also synthesize EPO, and its contribution may increase when the kidneys are unable to maintain adequate

Table 1 Postulated mechanisms of action of retinoid administration in animal models of kidney disease and reported human clinical trials

Drug	Animal model/disease/*n*		Outcome
Animal			
atRA	anti-Thy1.1 model rats	Mesangioproliferative glomerulonephritis	RA limits glomerular proliferation, glomerular lesions, and albuminuria. Marked reduction in renal TGF-β1. Reduction RAS activity[29]
atRA	HIV-1–transgenic mice	HIV associated kidney disease	atRA inhibits proliferation and induces differentiation in podocytes through RAR-mediated cAMP/PKA activation[28]
atRA	Streptozotocin-induced diabetic rats	Diabetic kidney disease	atRA decreases MCP-1 urinary excretion. Decreases proteinuria[34]
Tamibarotene	Male C57BL/6 mice	Unilateral ureteral obstruction	Inhibits the accumulation of fibrocytes and alleviates renal fibrosis mediated by IL-17A[64]
atRA	$Atg5^{flox/flox}$:Cagg-Cre mice	Cisplatin nephrotoxicity	RA activates autophagy and alleviates cisplatin acute kidney injury[37]
atRA	Male rats	Unilateral ureteral obstruction	ATRA treatment can increase the angiopoitin-1 and decrease interstitial fibrosis[65]
Human			
Isotretinoin	FSGS; MCD (shase II study)	12 (only 6 completed the study)	No complete or partial remission at 6 mo (clinicaltrials.gov)
Tamibarotene	Lupus nephritis (phase II study)	20	Not published

atRA: All-trans-retinoic acid; MCP-1: Monocyte chemoattractant peptide; FGFS: Focal segmental glomerulosclerosis; MCD: Minimal change disease; TGF-β 1: Transforming growth factor-β1; HIV: Human immunodeficiency virus; RA: Retinoic acid; IL: Interleukin.

levels for erythropoiesis[39]. ATRA is essential for hepatic production of EPO in early developmental stages and potentiates the EPO production through hypoxia-inducible factor signals and effectively improves renal anemia in mice[38].

Conclusions and future perspectives

The available evidence in cell cultures and animal models regarding the potential use of retinoids in the prevention and treatment of KD suggests that these compounds can effectively restore injured podocytes and decrease inflammation and interstitial fibrosis; however, a better understanding of retinoid signaling in renal cells is necessary to decreased toxicity and side effects of these compounds.

Vitamin E metabolism

Vitamin E is a fat-soluble vitamin and the most abundant liposoluble antioxidant compound in the human body; α-tocopherol accounts for about 90% of the vitamin E activity in human tissues. Vitamin E is emulsified by the bile acids and absorbed in the form of micelles in the small intestine; α-tocopherol is mostly transported from the blood to the liver cells by chylomicrons, very low-density lipoproteins (LDL), and high-density lipoproteins (HDL)[40].

The specific α-tocopherol transfer protein (α-TTP) mediates the transport from the hepatic lysosomes into lipoproteins, whereas the excessive α-tocopherol and other forms of vitamin E are excreted in bile. The primary function of α-TTP is to maintain normal α-tocopherol concentrations in plasma and extrahepatic tissues. α-TTP is also expressed in the placenta, brain, spleen, lung, and kidney[41]. Besides the lipoprotein-lipase action, the delivery of α-tocopherol to tissues takes place by the uptake of lipoproteins throughout their corresponding receptors[42].

Vitamin E is present in various foods and oils such as nuts, seeds, vegetable oils, green leafy vegetables, and fortified cereals. The recommended dietary allowance for males and females aged ≥ 14 years is 15 mg daily (or 22 IU). In most countries, vitamin E deficiency is not prevalent and is usually associated with irregularities in the absorption of dietary fat. Previous studies have shown that subjects with CKD do not have the recommended micronutrient intake; however, the KDIGO nutritional guidelines do not recommend routine vitamin E supplementation[43].

Vitamin E metabolism and effects on health and KDs

Vitamin E localizes in the cell membrane and plays a key role in the regulation of redox interactions. Furthermore, it is considered one of the most important defenses against membrane lipid peroxidation and superoxide generation. It is the major antioxidant present in human lipoproteins, acts as a peroxyl-radical scavenger, and is a potent suppressor of LDL lipid oxidation; lipid oxidation has been implicated

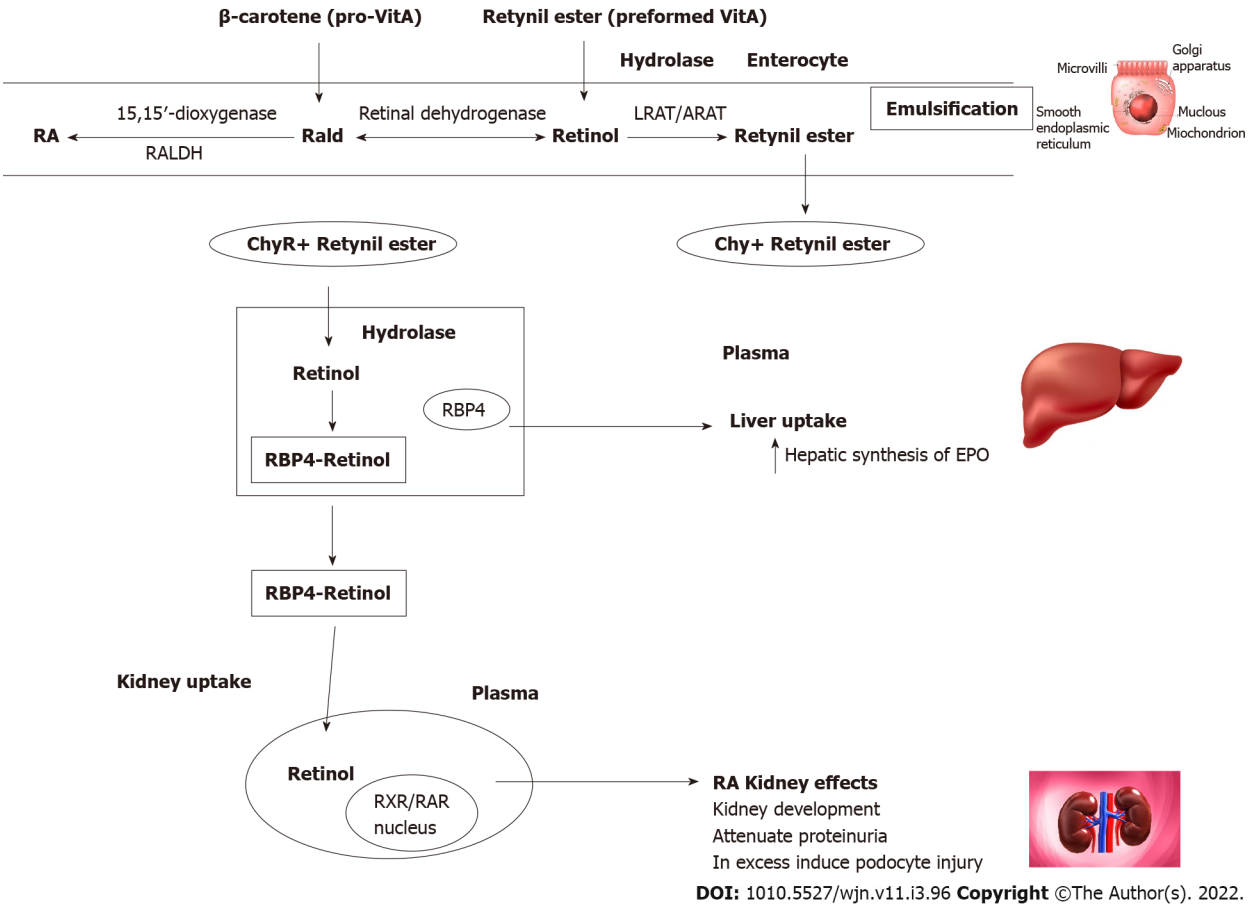

Figure 1 Retinoids restore injured podocytes that regulate the transition of parietal epithelial cells to podocytes in rat models of glomerular inflammation. LRAT: Lecithin retinol acyltransferase; RALDH: Retinal dehydrogenase; RBP4: Retinol binding protein 4; RA: Retinoic acid; EPO: Erythropoietin; VitA: Vitamin A; ARAT: Retinoic acid all-trans.

in chronic disease risk, including CVD and cancer[42,44]. Other important functions include the regulation of gene expression, improvement of immune response, inhibition of cell proliferation, and suppression of tumor angiogenesis[45]. In non-dialyzed and dialyzed CKD patients, plasma vitamin E levels are usually within the normal range; however, decreased α-tocopherol in red blood cell membranes of CKD subjects has been demonstrated[46].

Low levels of α-tocopherol in healthy subjects are associated with an increased risk for coronary artery disease[47], and higher intake has been shown to be protective; furthermore, recent studies suggest that higher α-tocopherol concentrations were related to a lower total mortality[48]. However, there is no information about tocopherol levels and mortality in CKD subjects, but some studies had been performed about vitamin E administration in this population.

Effects of vitamin E supplementation to ameliorate KD are controversial. The HOPE study found no beneficial effects of vitamin E administration on CVD mortality or renal complications[49]. Giannini *et al* [50] in a randomized trial in patients with Type 1 diabetes mellitus and persistent MA reported that vitamin E supplementation does not reduce albuminuria, but Khatami *et al*[51] found a significant decrease in urine protein excretion in T2 diabetic subjects.

The SPACE study performed in hemodialysis patients, found that high-dose α-tocopherol decreases the incidence of cardiovascular events but did not demonstrate a significant reduction in mortality[52]. Administration of α-tocopherol increases carboxy-ethyl-hydroxychromans with known potent anti-inflammatory and antioxidative properties[53], and a recent systematic review found that vitamin E administration reduces malondialdehyde in hyperactivity disorder (HD) patients; however, the effects on CVD or mortality were not particularly analyzed[54].

Vitamin E supplementation in HD subjects significantly improved the HDL function of cholesterol efflux capacity and in diabetic patients the endothelial function[55]. The use of vitamin E-coated dialyzer membranes may plausibly exert a site-specific scavenging effect on free radical species in synergy with reduced activation of neutrophils[56].

Vitamin E supplementation in CKD subjects is not recommended as has been shown to have no discernible effect on the overall mortality; one meta-analysis even demonstrated an increased mortality in healthy subjects who received a high dose of supplemented vitamin E[49,57]. Experimental and human clinical trials (Table 2) have demonstrated a role of vitamin E in preventing kidney injury. In the

Table 2 Reported human clinical trials of vitamin E administration in chronic kidney disease subjects

Ref.	*n*	Dose	Inclusion criteria	Outcome
Mann *et al*[49]	993	400 IU/d	1.4 ≤ SCr ≤ 2.3 mg/dL. Plus CV disease or DM	Follow-up 4.5 yr. No apparent effect on CV outcomes
Giannini *et al*[50]	10	1200 IU/d	Type 1 diabetes mellitus plus macroalbuminuria	Reduces markers of oxidative stress. No effect on MA
Khatami *et al*[51]	60	1200 IU/d	Diabetic nephropathy	Decrease in protein/creatinine ratio. Reduction in inflammatory markers
Boaz *et al*[52]	196	800 IU/d	Hemodialysis patients	Reduces CV disease
Himmelfarb *et al*[53]	30	300 IU/d	15 healthy subjects, 15 hemodialysis patients	Reduction on C reactive protein
Bergin *et al*[54]			Meta-analysis 16 papers	Reduction oxidative stress
Mune *et al*[55]	40	300 mg/d	Hemodialysis subjects	Improvement in endothelial function

CV: Cardiovascular.

subtotal (5/6) nephrectomy remnant kidney model in the rat, α-tocopherol has the capacity to modulate both tubulointerstitial injury and glomerulosclerosis, inhibit the expression of TGF-β, and reduce plasma and kidney malondialdehyde concentration[58].

Animal models have exhibited beneficial effects of vitamin E administration in the prevention of diabetic nephropathy by inhibition of the protein kinase C pathway and normalizing diacylglycerol cellular levels[59]. Tocotrienols are members of the vitamin E family with potent anti-oxidant activity; in *db/db* mice, T3β administration increased adiponectin levels and improved renal function[60].

Experimental immunoglobulin A nephropathy in rats is associated with increased renal oxidant injury, and dietary treatment with vitamin E has been reported to attenuate functional and structural changes[61]. The amelioration of renal injury by dietary α-tocopherol supplementation has also been observed in unilateral ureter obstruction[62] and puromycin aminonucleoside nephropathy[63]. There is still no robust evidence supporting the widespread use of vitamin E as a therapy for retarding chronic KD. Future studies with longer follow-up and larger sample size are necessary before any helpful recommendation.

CONCLUSION

RA and α-tocopherol have numerous cellular functions that can have an effect on kidney injury progression; however, further extensive research is needed before making clinical recommendations. Higher intake of natural carotenoids and tocopherols have been proven to have a beneficial impact on overall mortality, but supplementation with either of the two vitamins has not manifested any notable effect on the decrease in mortality of patients with CKD.

FOOTNOTES

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ORCID number: Maria Helena Rojo-Trejo 0000-0003-3435-9233; Ma Ludivina Robles-Osorio 0000-0002-3566-4646; Ernesto Sabath 0000-0002-4439-9098.

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MINIREVIEWS

Multidisciplinary basic and clinical research of acute kidney injury with COVID-19: Pathophysiology, mechanisms, incidence, management and kidney transplantation

Mohamed Wishahi, Nabawya M Kamal

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Mohamed Wishahi, Department of Urology, Theodor Bilharz Research Institute, Cairo 12411, Egypt

Nabawya M Kamal, Department of Anaesthesia and Surgical Intensive Care, Theodor Bilharz Research Institute, Cairo 12411, Egypt

Corresponding author: Mohamed Wishahi, MD, PhD, Doctor, Professor, Department of Urology, Theodor Bilharz Research Institute, Embaba, Giza, Cairo 12411, Egypt.
moh.weshahy@gmail.com

Abstract

Acute kidney injury (AKI) linked to coronavirus disease 2019 (COVID-19) has been identified in the course of the disease. AKI can be mild or severe and that is dependent on the presence of comorbidities and the severity of COVID-19. Among patients who had been hospitalized with COVID-19, some were admitted to intensive care unit. The etiology of AKI associated with COVID-19 is multifactorial. Prevention of severe AKI is the prime task in patients with COVID-19 that necessitates a battery of measurements and precautions in management. Patients with AKI who have needed dialysis are in an increased risk to develop chronic kidney disease (CKD) or a progression of their existing CKD. Kidney transplantation patients with COVID-19 are in need of special management to adjust the doses of immunosuppression drugs and corticosteroids to guard against graft rejection but not to suppress the immune system to place the patient at risk of developing a COVID-19 infection. Immunosuppression drugs and corticosteroids for patients who have had a kidney transplant has to be adjusted based on laboratory results and is individualized aiming at the protection of the transplanted from rejection.

Key Words: Acute kidney injury; COVID-19; SARS-CoV-2; Kidney transplantation; Dialysis; Immunosuppressant; Intensive care unit; Mortality; Cytokine storm

Core Tip: Acute kidney injury (AKI) in patients with coronavirus disease 2019 (COVID-19) is initiated by multifactorial events including direct viral effect, cardiac causes, thromboembolic phenomenon and cytokine storm. AKI is attributed to collapsing glomerulopathy, acute tubular necrosis and mitochondrial dysfunction. Management of AKI is multidisciplinary dependent on severity of COVID-19, associated comorbidities, intensive care unit admission and artificial ventilation. Management is initial control of fluid balance and in severe cases an early initiation of renal replacement and extracorporeal organ support which would support the organs and prevent disease progression. Kidney transplantation patients are at risk of developing AKI due to the state of their immunocompromised status caused by regular use of immunosuppressants; this situation indicates the adjustment of immunosuppressors in the condition of treatment of cytokine storm with corticosteroids.

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is caused by one of the coronaviridae family that has single-stranded RNA and causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2022, following its rapid worldwide spread, the World Health Organization recognized the disease as a pandemic[1].

COVID-19 initially affects the lungs, but it also affects other organs including the heart, intestine, and the kidneys and causes acute kidney injury (AKI). Up to 25% of patients who had severe COVID-19 developed AKI[2,3]. Since 2019, the new variants of SARS-CoV-2 have been identified and these new variants have similar effects and can cause AKI.

Acute kidney injury due to COVID-19 is multifactorial and this includes cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of the immune system, hypercoagulopathy and endotheliosis, collapsing glomerulopathy and thrombotic microangiopathy[4-6].

Risk factors for AKI in patients with COVID-19 are older age, obesity, diabetes, hypertension, heart failure, chronic kidney disease, immunosuppression status and cancer chemotherapy. Additional factors are anemia, lymphopenia, leukocytosis, an increase in inflammatory markers (D-dimer and IL-6) and the need for mechanical ventilation and vasoactive drugs which all can aggravate the condition.

AKI is a complication of SARS-CoV-2 Infection and presents as mild or severe and is ranged from grade 1 to grade 3. AKI could be managed conservatively or the patient will be in need of hemodialysis which is dependent on severity. 10%-15% of all hospitalized patients had some degrees of AKI but patients in the intensive care unit (ICU) experienced an incidence that would exceed 50%[10].

The hemodialysis initiation timing depends on the severity of AKI and continuous venous-venous hemodiafiltration is preferable for patients requiring vasoactive drug infusion and/or having hypervolemia.

Kidney transplant recipients are at considerable risk for development of AKI due to chronic immunosuppression. Patients who had kidney transplantation and develop COVID-19 are on maintenance immunosuppressant drugs including corticosteroids and the doses of steroids should be adjusted for every case independently.

PATHOPHYSIOLOGY AND MECHANISM OF COVID-19-INDUCED AKI

Acute kidney injury due to COVID-19 is multifactorial including cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of immune system, hypercoagulopathy and endotheliosis. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 which are present in the kidney are targeted by SARS-CoV-2 causing AKI. In the glomerulus, podocytes and endothelial cells have been found to be the sites for viral infection resulting in podocyte dysfunction that effects glomerular filtration leading to proteinuria and hematuria. Viral infection of endothelial cells leads to changes in glomerular capillary hemostasis that cause fibrin thrombi. SARS-CoV-2 was detected in the proximal tubular cells and was attributed to vacuolar degeneration and loss of the brush border of tubular epithelial cells. The tubular lumen contains necrotic epithelium and the interstitium shows massive macrophage infiltration. Other non-viral mechanisms that contribute to AKI includes focal segmental glomerulosclerosis, hemodynamic factors, cardiac dysfunction, high levels of mechanical

ventilation, hypovolemia secondary to decreased fluid intake, fever, sepsis and the use of nephrotoxic antibiotics.

Cardiac factors

COVID-19 pneumonia can cause right ventricular failure and lead to kidney congestion and finally AKI. Left ventricular dysfunction can lead to hypotension, decreased cardiac output and hypo perfusion of the kidneys and ultimately AKI[4].

Direct effects of COVID-19 virus on the kidney

The virus particles were reported to be present in renal endothelial cells, indicating viraemia as a cause of endothelial damage and a probable contributor to SARS-CoV-2 infecting the renal tubular epithelium and podocytes through ACE2 and causing acute tubular necrosis, collapsing glomerulopathy, mitochondrial dysfunction, protein leakage in Bowman's capsule and protein reabsorption vacuoles[5-7].

Cytokine stroke

Cytokines can alter the immune response and the development of lymphopenia. Hypercoagulability occurs that will cause microthrombi and microemboli ultimately leading to stroke.

Rhabdomyosis

Severe COVID-19 can lead to skeletal muscle damage leading to myoglobulin release which induces renal damage through formation of pigment casts that cause tubular obstruction and iron release that has a direct effect on tubular toxicity. Myoglobulin casts have been demonstrated in renal tubules[8,9].

Sepsis

Systemic inflammation due to sepsis leads to release of multiple molecular patterns that are damaging and pathogen-associated that enters the bloodstream and is filtered at the glomerulus.

Hypoxemia and dehydration

Hypoxemia and dehydration are caused by high fevers, fluid restriction and diuretics that are used for the management of acute respiratory distress syndrome. This is combined with mechanical ventilation which reduces renal perfusion.

Hypercoagulable state

It attributes to injury of renal microvasculature.

Macrophage-activation syndrome

Macrophage-activation syndrome involves cytokine storm and high plasma ferritin, which lead to AKI [10].

Direct effect of SARS-CoV-2 virus on tubular epithelium

The SARS-CoV-2 virus binds with ACE2 which is highly expressed in the kidney and there is also high expression in podocytes[11]. Direct viral infection is highly probable to contribute to injury mechanisms. Autopsies from 6 patients who died due to COVID-19 associates AKI and showed that kidney tissues, on light microscopy, exhibit severe acute tubular necrosis, infiltration of tubular interstitium with $CD68^+$ macrophage and deposition of C5b-9. An immunohistochemistry study demonstrated the presence of SARS-CoV-2 nucleocapsid protein in the kidneys[12]. High viral RNA titers were demonstrated in the kidneys[23]. Electron microscopic examination elicited clusters of SARS-CoV-2 particles with its distinctive spikes in the tubular epithelium and podocytes. The pathological changes of the kidney in AKI associated with COVID-19 include vascular, glomerular and tubulointerstitium damage.

Vascular events

Vasoconstriction of intrarenal vessels increased vascular permeability, formation of microthrombi and vascular endothelium damage. These events contribute to development of AKI[13].

Glomeruli

Autopsy studies of the kidneys of patients who died from COVID-19 showed focal and diffuse fibrin thrombi in glomerular capillaries, collapsing glomerulopathy, glomerular epithelial damage, loss of podocytes integrity with hyperplasia and hypertrophy of the glomerular epithelium, endothelial injury, erythrocyte stagnation in the glomerular capillary with glomerular loop occlusion by erythrocytes[14].

Proximal tubules

Autopsies from kidneys of COVID-19 patients shows on light microscopy diffuse kidney injury. The renal tubules showed loss of the brush border and necrosis associated with tubulointerstitial fibrosis

and vacuolar degeneration. Electron microscopy studies shows SARS-CoV-2 viruses were demonstrated in the tubular epithelium of the proximal tubule and podocytes[13,14].

Interstitium

It shows inflammatory cell infiltration and edema that is attributed to the increased permeability of the endothelium and leakage of the glomerular filtrate in the tubules to the interstitium[14].

Inflammation and thrombotic microangiopathy

COVID-19 initiates the release of a vast number of pro-inflammatory cytokines known as the cytokine storm syndrome (CSS) and can lead to multiple organ dysfunctions. It would also lead to endothelial dysfunction and a pro-thrombotic event that leads to small vessel vasculitis and extensive microthrombosis. A condition known as thrombotic microangiopathy is one of the main causes of mortalities in COVID-19. Its development might be mediated by inflammation, endothelial dysfunction and microthrombosis. Interleukin-6 (IL-6) has a critical leading role in CRS. An increase in plasma levels of IL-6 in patients with COVID-19 denotes a worse prognosis. CSS may cause renal medullary hypoxia and tubular cell damage that demonstrate the close relationship between the lungs and the kidneys[15-20].

INCIDENCE OF AKI LINKED TO SARS-CoV-2 INFECTION

Acute kidney injury is a complication of SARS-CoV-2 Infection and it can happen in either moderate or severe cases of COVID-19. AKI can manifest as a mild or more severe form. It could be managed conservatively or the patient may be in need of hemodialysis. Incidence of AKI of all hospitalized patients is 10-15% with varying degrees of severity while for patients in the ICU, the incidence can be higher and exceed 50%[10].

The development of AKI in patients with COVID-19 depends on the level of severity and whether they are outpatient, hospitalized or in the ICU. The incidence of AKI during a hospital stay is reported with a range of [11% (8%-17%)]. In the critically ill patient, the range is [23% (14%-50%)][20,21].

Several studies have reported the prevalence of AKI in COVID-19 patients. These studies are case series, observational study, retrospective single-center study, prospective cohort study and retrospective observational cohort study. The studies implemented the definition of acute kidney injury adopted by "Kidney Disease: Improving Global Outcome (KDIGO)"which is defined as an increase in the serum creatinine level up to 1.5 times the baseline level or an increase of at least 0.3 mg/dL within the past 48 h. Another useful definition of AKI was one established by the "Acute Kidney Injury Network" (AKIN) where the criteria of AKI is defined as an increase in the serum creatinine level up to 1.5 times the baseline level or an increase of at least 0.3 mg/dL within the past 48 h (Table 1)[21-29].

An established diagnosis of COVID-19 infection is by a positive PCR test for SARS-CoV-2, elevated laboratory values of D-dimer > 0.5 μg/ml, fibrinogen, ferritin, LDH, CK, CRP, serum creatinine, cystatin C, and hematuria with urine deposits, decreased eGFR, mL/min per 1.73 m^2, and computerized tomography (CT) of the chest that shows a round glass appearance. The incidence of AKI in published data ranges from 4.5% to 36.6%. The real incidence of AKI in COVID-19 remains uncertain due to a lack of reported studies.

In a retrospective Brazilian study on 102 patients who had COVID-19 and were admitted to the ICU, AKI was diagnosed in 54 (56.8%) of the cases that was grade 1 in 22.2%, being KDIGO 1; grade 2 in (7.4%), and grade 3 in (70.3%). Patients with grade 3 AKI were older adults (64.9 ± 15.1 years of age) and had comorbidities of diabetes and hypertension. Patients who had an immunosuppression condition secondary to chemotherapy treatment for cancer were (11.6%). Patients who had chronic kidney disease stages 2-4 were (16.8%). Patients who had comorbidities and developed AKI had received mechanical ventilation and vasoactive drugs that reflected the severity of the disease. Patients requiring hemodialysis were hypertensive, diabetic and immunosuppressed.

Patients under dialysis and/or on vasoactive drugs have a higher indication rate of mechanical ventilation (93, 8% *vs* non dialysis 38, 1%). Continuous renal replacement therapy was initiated in 26 patients (81.3%) out of 32 patients who were submitted to dialysis therapy. Eleven patients (34.4%) who received dialysis died, while 21 (65.6%) experienced recovery of renal function with maintained glomerular filtration rate. When comparing patients who died to those who are still alive and both had AKI due to COVID-19, it was found that those who died were older, diabetic, immunosuppressed, received mechanical ventilation and were on vasoactive drugs with a range of: (78.6 *vs* 61.9 years of age), (47.1 *vs* 23.1%), (29.4 *vs* 7.7%), (88.8 *vs* 72.2%), (94.1 *vs* 48.7%) respectively[29].

MANAGEMENT OF AKI RELATED TO COVID-19

Basic patient data for the planning of management in AKI linked to COVID-19 are gender, age, the

Table 1 Incidence of acute kidney injury linked to severe acute respiratory syndrome coronavirus 2 infection

Ref.	Country	Type of study	Coronavirus disease patients , *n*	Patients admitted to intensive care unit, *n* (%)	Patients developed acute kidney injury, *n* (%)
Arentz *et al* [22], 2020	United States	Case series	21	4 (19.1)	4 (19.1)
Hirsch *et al* [23], 2020	United States	Retrospective observational cohort study	5449	1395 (25.6)	1993 (36.6)
Thakkar *et al* [24], 2020	United States	Retrospectiveobservational study	300	300	224 (75)
Yidirim *et al* [25], 2021	Turkey	Retrospective study	331	17	17 (5.1)
Yan *et al*[26], 2020	China	Retrospective, observational cohort study	882	105 (11.9)	115 (13)
Zhang *et al* [27], 2020	China	Case series	221	55 (24.8)	10 (4.5)
Chen *et al*[28], 2020	China	Case series	274	50 (18.5)	29 (11)
Cheng *et al* [29], 2021	China	Prospective cohort study	701	73 (10.4)	36 (5.1)
Neves *et al* [30], 2021	Brazil	Retrospective study	102	95	54

presence of comorbidities such as diabetes mellitus, hypertension, CKD, presence of chronic obstructive pulmonary disease, associated malignancies and maintenance medications with immunosuppression drugs. Laboratory tests for COVID-19 are: D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, blood count, reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 virus, blood urea, serum creatinine, liver function tests, ECG, echo cardiogram, and chest CT. AKI is defined according to the KDIGO criteria which is based on the creatinine values and urine output. The classification of AKI by KDIGO is 1, 2, or 3 according to clinical and laboratory data.

AKI KDIGO 1 is an increase of creatinine ≥ 0.3 mg/dL or 1.5-1.9 times baseline and/or urine output < 0.5 mL/kg/h for 6-12 h.

AKI KDIGO 2 is an increase of creatinine of 2.0-2.9 times baseline and/or urine output < 0.5 mL/kg/h for 12 h.

AKI KDIGO 3 is an increase of creatinine of 3.0 times baseline or an increase in serum creatinine to ≥ 4.0 mg/dL and/or urine output < 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h, or initiation of renal replacement therapy (RRT).

Consideration includes medications for COVID-19: anti-IL6, ivermectin, and nitazoxanide. Ultimate evaluation of patients with AKI due to COVID-19 is: days of ICU stay, period of mechanical ventilation time and total hospitalization period.

The hemodialysis initiation timing depends on the severity of AKI. A hemodialysis catheter of 15.5 Fr is placed in the patients with continuous venous-venous hemodiafiltration and is preferable for patients requiring vasoactive drug infusion and/or having hypervolemia. The recommended dialysis dose is 25-30 mL/kg/h with regional citrate anticoagulation. For patients who do not need a vasoactive drug infusion, they would be on classic hemodialysis[29].

Measures to be considered in the management of Covid-19 and patient in the ICU to stabilize kidney function and to avoid AKI

Nephrotoxic drugs should be avoided; serum creatinine and urine output are regularly monitored.

Initiation of lung-protective ventilation to avoid hemodynamic changes and to diminish the sequences of cytokine burden on the kidneys[30].

Avoid volume overload that reduces the risk of pulmonary edema. Fluid balance should be adjusted according to volume responsiveness, restoration of normal volume status should avoid right ventricular overload, congestion and subsequent AKI.

Hypovolemia should be corrected to prevent AKI.

Renal replacements therapy and extracorporeal support

Renal replacements and extracorporeal support are indicated in case conservative management fails. Patients with volume overload should be considered for RRT. Patients with nonresponding hypoxemia are candidates for extracorporeal support. Early initiation of RRT and extracorporeal organ support (ECOS) will support the organs and prevent progression of COVID-19 and AKI[31].

Hypercoagulable state

Severely ill patients with COVID-19 often have a hypercoagulable state and anticoagulation protocols for the extracorporeal circuit should be implemented[32].

Cytokine storm

The application of hemoperfusion with sorbent cartridges might prevent cytokine-induced kidney damage[33].

Lung-protective ventilation

Ventilation is applied with appropriate tidal volume to avoid hypercapnia, respiratory acidosis, increased need for vasopressors and in severe cases of AKI. In these patients, extracorporeal carbon dioxide removal ($ECCO_2R$) might help to prevent progression of severity[34].

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation is indicated in cases where respiratory exchanges further deteriorate.

Bacterial infection

Patients with SARS-CoV-2 can develop a sepsis-like syndrome. The use of sequential extracorporeal therapies for immunomodulation and endotoxin and cytokine removal, extra corporeal organ support (ECOS) for various organs should be considered, as clinical progression can be rapid[33].

KIDNEY TRANSPLANTATION DURING COVID-19

Kidney transplant recipients (KTRs) are at considerable risk for development of AKI due to the maintenance use of immunosuppression and in addition to co-morbidities[35,36].

Since the Covid-19 pandemic, there is a significant reduction of kidney transplantation procedures[37,38].

Presentation of COVID-19 in this specific group of patients is fever and cough; atypical presentation is gastrointestinal symptoms. In a series of KTRs showed that the median age (51-62 years), duration between transplantation to diagnosis of COVID-19 was ranged from 2 years to 3 years. It is reported in two series that 2 patients had positive data of COVID-19 after 3 mo of kidney transplantation[39,40].

Indication for mechanical ventilation in KTRs who had COVID-19 was (22%-91%), while mortality rate was (7%-30%). These KTRs who had COVID-19 were on maintenance immunosuppression. Patients who had AKI was (30%-57%) and the need of with variable rates of RRT were (5%-43%). Mortality rate was as high as 32% (Table 2)[35,40-46,48].

Patients who had kidney transplantation and are COVID-19 positive while on steroids as a part of their maintenance immunosuppression because cessation would not be recommended, should have their dose adjusted depending on their personal case.

Patients who had transplantation and are on immunosuppressant corticosteroids and tacrolimus (TAC or FK506), the oral fast release of TAC is (Prograf) which is a calcineurin inhibitor employed to reduce the risk of acute rejection and allograft loss. For Tacrolimus and corticosteroids, the dose would be manipulated according to the level of FK506 in the blood which has been found to be decreased in patients who had a COVID-19 infection, consequently, the doses of tacrolimus and corticosteroid will be increased. Myfortic (mycophenolic acid) is an immunosuppressant that is given with cyclosporine and corticosteroid to prevent organ rejection after a kidney transplant. It weakens the immune system that helps to prevent kidney rejection. Myfortic should be stopped while tacrolimus and corticosteroids should be increased in cases where a patient who had kidney transplant and also have COVID-19 infection. Doses of myfortic and corticosteroids will be manipulated according to the regular laboratory data to guard against severity of COVID-19 and avoidance of kidney rejection.

CONCLUSION

Acute kidney injury in patients with COVID-19 is initiated by multifactorial etiopathology events including direct viral effect, cardiac causes secondary to right sided heart failure and cardiomyopathy, thromboembolic phenomenon, vascular factors, cytokine storm, toxic drugs to the kidney that are given during treatment of pneumonia from COVID-19. Pathophysiology of AKI is attributed to collapsing glomerulopathy, acute tubular necrosis, mitochondrial dysfunction and arterial occlusion.

Management of AKI is a multidisciplinary approach and should be personalized depending on several factors: severity of COVID-19 disease, ICU admission, induction of artificial ventilation and associated comorbidities. Patients who have all of these elements will have severe AKI and management is to preserve kidney function and prevent aggravation of the disease.

Table 2 Demographic data of kidney transplant recipients who had severe acute respiratory syndrome coronavirus 2 and developed acute kidney injury and the incidence of survival vs mortality

Study	*n*	Median age, yr	Median Transplant, yr	Acute kidney injury incidence, %	Renal replacement therapy, %	Mechanical ventilation, %	Mortality, %
Banerjee *et al*[40], 2020	7	54	2	57	43	14	14
Nair *et al*[42], 2020	10	57	7.7	50	10	40	30
Columbia *et al* [43], 2020	15	51	4	40	14	27	7
Alberici *et al*[35], 2020	20	59	13	30	5	0	25
Akalin *et al* [48], 2020	36	60	NR	NR	21	39	28
Lubetsky *et al* [44], 2020	54	57	4.7	51	10	28	13
Cravedi *et al*[41], 2020	144	62	5	52	NR	30	32
Caillard *et al*[45], 2020	279	62	5	44	11	30	23
Elias *et al*[46], 2020	6	54	NR	42	11	22	24

NR: Not reported.

Main treatment steps are to control fluid balance in severe cases and an early initiation of renal replacement and extracorporeal organ support which would support the organs and prevent progression of COVID-19 and AKI.

Kidney transplantation patients are at risk of developing AKI due to the immunocompromised status caused by regular doses of immunosuppressants. This situation indicates modification of immunosuppressors and the setting of treatment of cytokine storm with corticosteroids. In specific cases, there is an indication to stop myfortic immunosuppressant and to increase corticosteroid and modify the dose of tacrolimus.

Patients who are in regular hemodialysis need to adjust the anticoagulant dose when the patient receives anticoagulant to treat or prevent the hyper coagulopathy state resulting from COVID-19.

FOOTNOTES

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Country/Territory of origin: Egypt

ORCID number: Mohamed Wishahi 0000-0002-4559-619X; Nabawya M Kamal 0000-0003-0573-353X.

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WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc*.

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MINIREVIEWS

New antigens involved in membranous nephropathy beyond phospholipase A2 receptor

Maurizio Salvadori, Aris Tsalouchos

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Maurizio Salvadori, Department of Renal Transplantation, Careggi University Hospital, Florence 50139, Tuscany, Italy

Aris Tsalouchos, Division of Nephrology, Santa Maria Annunziata, Florence 50012, Tuscany, Italy

Corresponding author: Maurizio Salvadori, MD, Professor, Department of Renal Transplantation, Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Tuscany, Italy. maurizio.salvadori1@gmail.com

Abstract

When the physiopathology of membranous nephropathy was first described, almost 30% of cases were recognized to be secondary to well-known diseases such as autoimmune diseases, tumors or infections. The remaining 70% cases were called primary membranous nephropathy as the exact mechanism or pathogenic factor involved was unknown. The discovery of the M type phospholipase A2 receptor and thrombospondin type 1 domain containing 7A as causative antigens in these "so called" primary membranous nephropathies provided new insights into the effective causes of a large proportion of these cases. Novel techniques such as laser microdissection and tandem mass spectrometry as well as immunochemistry with antibodies directed against novel proteins allowed the confirmation of new involved antigens. Finally, using confocal microscopy to localize these new antigens and immunoglobulin G and Western blot analysis of serum samples, these new antigens were detected on the glomerular membrane, and the related antibodies were detected in serum samples. The same antigens have been recognized in some cases of secondary membranous disease due to autoimmune diseases, tumors and infections. This has allowed examination of the relationship between antigens in primary membranous nephropathy and their presence in some secondary nephropathies. The aim of this study is to describe the characteristics of the new antigens discovered and their association with other diseases.

Key Words: Membranous nephropathy; Exostosin ½; Neural cell adhesion molecule 1; Neural epidermal growth factor like-1 protein; Protocadherin 7; Semaphorin 3B

Core Tip: The pathophysiological mechanisms of membranous nephropathy have been partially known for a long time. Novel techniques have allowed identifying several antigens and the corresponding antibodies as the main cause of a large part of these diseases. Therefore, a large part of membranous nephropathy, once called primary, are due to immune complexes whose components are now recognized. The same antigens have been recognized in a part of secondary membranous disease, which are due to autoimmune diseases, tumors and infections, diseases. This fact allows a relationship between antigens found either in primary membranous nephropathy or in some forms of secondary nephropathies.

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INTRODUCTION

Membranous nephropathy (MN) is a rare disease that affects podocytes and is characterized by the accumulation of immune deposits on the subepithelial side of the glomerular capillary wall. These immune deposits consist of immunoglobulin (Ig) G directed against antigens that have long remained unknown. MN is referred to as primary MN when there is no association with a known disease (70% of cases) or secondary MN when MN occurs in association with clinical conditions such as autoimmune diseases, tumors, infections and hepatitis B (30% of cases). Two studies in 2009 and 2014 allowed us to identify causal antigens involved in primary MN[1,2]. A related study reported the first human podocyte antigen in a rare subset of infants born with MN that developed because the mother was deficient in neutral endopeptidase (NEP) due to a truncating mutation in the *MME* gene coding for NEP [3,4]. The first antigen, identified in 2009, is the M type phospholipase A2 receptor 1. The antigen recognized in the 2014 study is thrombospondin type 1 domain containing 7A (THSD7A)[1,2]. Using Western blotting and mass spectrometry, THSD7A was identified in serum samples from patients with MN. Additionally, immunohistochemical analysis of biopsy samples from the same patients revealed that THSD7A localized to podocytes, and immunoglobulin G (IgG) eluted from these samples was specific for THSD7A.

Phospholipase A2 receptor (PLA2R) and THSD7A are involved in 70% and 5% of primary MN cases respectively (Figure 1).

These antigens were thought to be specific to primary MN, but were also later found in patients with MN related to hepatitis B infection and sarcoidosis[5-7].

Novel techniques

Recently, an approach using laser microdissection and tandem mass spectrometry (MS/MS) enabled the detection of novel proteins in glomerular diseases. MS/MS can identify approximately 1500-2000 proteins in glomerular extracts and allows semiquantitative measurements.

Briefly, these techniques were used to identify proteins with high spectral counts in PLA2R-negative MN patients and control patients with different nephropathies. This new protein was identified, using immunochemistry with antibodies directed against the new protein, which revealed membranous staining along the glomerular basement membrane (GBM), confirming a new antigen involved in MN.

Finally, using confocal microscopy to localize the new antigen and IgG and Western blot analysis of serum samples, we detected the new antigen on the glomerular membrane and the related antibody in serum samples[8].

The aim of this study is to describe the characteristics of the new antigens discovered principally thanks to these novel techniques and to clarify their association with other diseases.

Exostosin 1/ 2 associated MN

An examination of both serum samples and glomerular eluates from patients with the so- called idiopathic MN negative for PLA2R with these new techniques revealed the first novel antigens, namely exostosin 1 and exostosin 2 (EXT1 and EXT2, respectively).

EXT1/EXT2-positive MN cases were more common in females (80.9 with a mean age of 35.7 years) [8]. In the first report, the mean serum creatinine and proteinuria levels at presentation were 1 mg% and 5.9 g/24 h, respectively. A total of 70.8% of patients had abnormal laboratory values for antinuclear antibodies, double-stranded DNA antibodies, anti-Smith antibodies or anti-Sjogren syndrome-related antigen A or B[9]. Thirty-four percent of patients had a clinical diagnosis of systemic lupus erythematosus.

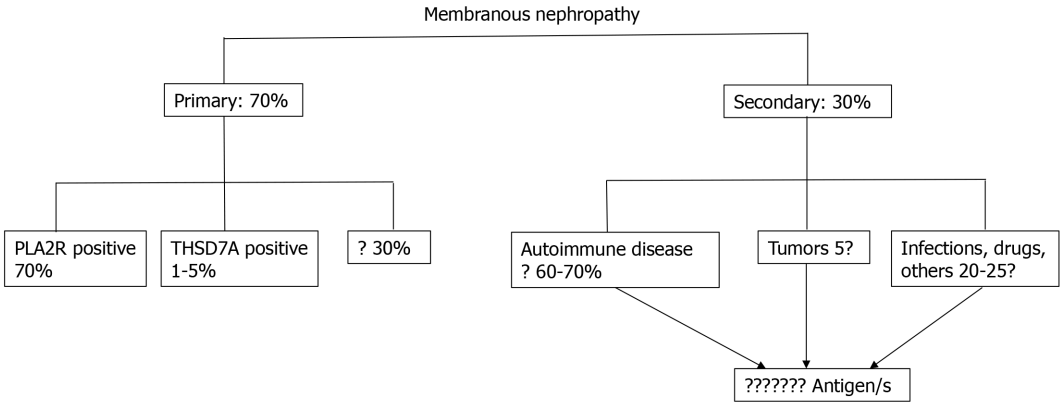

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Figure 1 Membranous nephropathy. Old classification of membranous nephropathy. PLA2R: Phospholipase A2 receptor; THSD7A: Thrombospondin type 1 domain containing 7A.

Based on MS analysis, all four classes of IgG were present in patients with EXT1/EXT2-positive MN with IgG1 the most abundant, followed by IgG2, IgG3 and IgG4. In addition to IgG and C3, 84% of patients exhibited staining for IgA or IgM. Seventy-three percent of patients showed staining for C1q on immunofluorescence, and all patients showed subepithelial deposits. Mesangial deposits were also present in 96% of patients. Subendothelial deposits were less frequently found.

Tubulointerstitial inclusions were present in 80% of patients.

The GBM is composed of mostly type IV collagen, laminin, nidogen and heparan sulfate proteoglycans. Agrin and perlecan are the main heparan sulfate proteoglycans in GBM. Heparan sulfate proteoglycans are present in the basement membrane and matrix and on cell surfaces.

EXTs are glycosyltransferases responsible for the synthesis of heparansulfate, through the addition of glycosaminoglycan residues to the core protein. The result is the generation of complex polysaccharides, which explains why these two proteins are found together[10,11].

EXT1 and EXT2 show structural similarities, and EXT1 and EXT2 can exist as a heterodimers and act as a copolymerases in heparan sulfate chain elongation. The EXT1/EXT2 heterodimer also has increased stability and activity compared to those of the individual proteins, which are transmembrane proteins.

EXTs are secreted into the extracellular medium in a truncated form[12]. Five genes encode EXT proteins: *EXT1, EXT2, EXTL1, EXTL2* and *EXTL3*[13]. Mutations in *EXT1* and *EXT2* generate hereditary multiple exostoses, one of the most common inherited skeletal disorders[14].

To date, it is still difficult to detect circulating anti-EXT1/EXT2 antibodies. This difficulty may be because serum antibodies target truncated EXT proteins or are present at a very low titer.

In a recent study, EXT1/EXT2 were present in 33% of a cohort of patients with membranous lupus nephritis[15]. Compared with EXT1/EXT2-negative membranous lupus nephritis, EXT1/EXT2-positive disease appears to represent a subgroup with favorable kidney biopsy findings with respect to chronicity indices. Indeed, cases of membranous lupus nephritis that are EXT1/EXT2 negative are more likely to progress to end-stage kidney disease (ESKD) than those that are EXT1/EXT2 positive.

In conclusion, using proteomics and immunochemistry, the authors found EXT1/EXT2 in the GBM of PLA2R-negative MN patients. Clinical and biopsy findings showed features of autoimmune disease, including lupus nephritis in 8% of patients[16].

Neural cell adhesion molecule 1

Neural cell adhesion molecule 1 (NCAM1) is a member of the IgG superfamily of proteins that was identified using the techniques described above[17]. NCAM1 colocalizes with IgG within glomerular immune deposits, and antibodies against NCAM1 could be detected in patient sera. NCAM1 was predominantly expressed in membranous lupus nephritis patients but was also found in 2% of primary MN patients. Many lupus nephritis patients with NCAM1 were also positive for EXT2. NCAM patients were also positive for IgA, IgM and C1q. Neuropsychiatric disease occurred in 40% of NCAM-positive patients, probably due to NCAM1 expression in the central nervous system[18].

Neural epidermal growth factor-like 1 protein

Neural epidermal growth factor-like 1 protein (NELL-1) is a secreted, 90-kDa protein expressed in osteoblasts that promotes bone regeneration[19]. The NELL-1 gene is named after its similarity to a gene called *Nel* that is strongly expressed in neural tissue and encodes a protein with epidermal growth factor (EGF)-like repeats (Figure 2)[20].

In the kidney, NELL-1 expression is increased in tubules and detectable in the glomeruli, as 20% of glomerular cells express NELL-1 at the RNA level[21,22].

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Figure 2 Structure of neural epidermal growth factor-1 protein. TSPN: TSP-1-like domain; C-C: Coiled coil domain; VWC: Von Willebrand factor type C domain; EGF: EGF-like domains E.

Sethi *et al*[23] suggested that NELL-1 is associated with MN.

The authors selected PLA2R-negative MN patients and identified this novel NELL-1 protein by laser microdissection and MS. Granular anti -NELL-1 GBM staining was documented using immunohistochemistry, and NELL-1 and IgG colocalization was observed by confocal microscopy. Finally, serum antibodies against NELL-1 were detected by Western blotting. Sethi *et al*[23] concluded that NELL-1 positive MN is a distinct type of MN. The authors suggested that NELL-1 is shed from podocytes rather than entrapped from circulating antigens or immune complexes[24].

Most importantly, Sethi's finding was confirmed by validation in a French cohort and a Belgian cohort.

Kidney biopsy specimens from patients with NELL-1-associated MN showed features of MN with a thickened GBM as well as IgG and C3 expression. IgG subtyping revealed predominantly IgG1. In a subset of the biopsy specimens, a segmental GBM distribution of immune deposits was observed by immunofluorescence and electron microscopy[25].

In particular, *Kudose et al*[25] examined 2003 MN patients without lupus. Fifty of them showed segmental MGN (sMGN) defined by subepithelial deposits involving 25%-75% of the GBM. Among these cases with sMGNs, NELL-1 staining was present in 25%. PLA2R, THSD7A and EXT 1 were negative in all cases evaluated.

Among 21 patients with sMGN at follow-up, 7/21 patients had received immunosuppression, 86% had stable improved renal function, and 60% had complete (45%) or partial (15%) remission of proteinuria. Accordingly, MGN is a rare PLA2R-negative variant of MN with NELL-1 positivity in 29% of patients and favorable prognosis, even in the absence of immunosuppressive treatment.

According to this study, NELL-1 appears to be the first antigen in segmental MN.

In a recent study, Caza *et al*[26] found that NELL-1 is a target antigen associated with MN malignancy. They found active or metastatic malignancy in 33% of patients with NELL-1-associated MN. Additionally, they found NELL-1 positivity within glomeruli and a tumor from the same patient affected by invasive ductal carcinoma of MN in the breast.

The authors concluded that NELL-1, a recently identified antigen in MN, is enriched in patients with malignancy-associated MN, and anti-NELL-1 antibodies can be detected within the serum of these patients.

Finally, a recent study by Spain *et al*[27] found that in patients administered lipoic acid for different conditions, high-grade proteinuria could appear. These patients may have NELL-1-associated MN, and the discontinuation of lipoic acid could result in proteinuria remission.

Semaphorin 3B-associated MN

Semaphorin 3B (SEMA 3B) is a recently discovered target antigen that has been principally detected in pediatric patients, particularly very young children[8]. The mean age of these pediatric patients was 6.9 years, and approximately half of SEMA 3B-associated MN was detected in children < 2 years. Among all

Table 1 Clinical findings in Semaphorin 3B-associated membranous nephropathy[8,28,29]

Case	Age (yr)/sex	UP (g/24)	Serum CR (mg/dL)	Remission	Serum CR/UP/24 h
1	41/F	7.9	0.74	Spontaneous	0.6/no proteinuria (16 mo)
2	26/F	6.2	0.4	Spontaneous	0.43/400 mg (18 mo)
3	2/M	5	0.5	Immunosuppressive	0.35/150 mg (24 mo)
4	40/F	17.3	0.9	Immunosuppressive	0.6/no proteinuria (10 yr)
5	19 mo/M	0.4	0.7	Immunosuppressive	0.9/400 mg (18 mo)
6	2/F	UP/CR ratio 6.81	0.21	Immunosuppressive	UP/CR ratio 0.23 (13 mo)
7	17/M	UP/CR ratio 0.78	0.6	Immunosuppressive	UP/CR ratio 0.1 (19 mo)
8	9 mo/M	UP/CR ratio 0.94	0.45	Immunosuppressive	UP/CR ratio 0.09 /14 yr)
9	2/M	UP/CR ratio 1.95	0.13	Immunosuppressive	UP/CR ratio 0.12 (5 yr)
10	14/M	3	0.64	Lost to follow up	n/a
11	16/M	12	0.83	Immunosuppressive	Dialysis

F: Female; M: Male; UP: Urinary protein; CR: Creatinine.

patients, SEMA 3B-associated MN is rare and accounts for 1%-3% of all MNs. In the pediatric group, it accounts for approximately 15% of MN cases.

After the initial identification of three pediatric patients, an additional eight cases of SEMA 3B-associated MN were identified in validation cohorts from France and Italy[8]. To date, 11 patients with SEMA 3B-associated MN, including three adults have been identified[28].

Using laser dissection and MS/MS, SEMA3B was detected in PLA2R-negative MN biopsies[29].

Semaphorins are a group of secreted and transmembrane/membrane-bound proteins containing a conserved extracellular semaphorin (sema) domain of approximately 500 amino acids that is characterized by highly conserved cysteine residues[30-32].

More than 20 semaphorins have been identified and divided into 8 subclasses. SEMA 3B is a secreted protein with a sema domain, a plexum-semaphorin-integrin domain, an Ig domain and a basic domain (Figure 3).

The semaphorin 3 family and its receptors have been detected in endothelial cells, podocytes and tubular epithelial cells[33]. In SEMA 3B-associated MN, bright granular capillary wall staining for SEMA 3B along the GBM have been documented, and SEMA 3B may be found using immunofluorescence microscopy. Confocal immune fluorescence microscopy analysis has shown the colocalization of SEMA 3B and IgG in glomerular immune deposits.

Using Western blot analysis, anti-SEMA 3B antibodies have been detected in patients with SEMA 3B-associated MN. The SEMA 3B autoantibody can recognize a cryptic epitope that is unmasked by disruption of disulfide bonds.

Clinical findings in SEMA 3B-associated MN are shown in Table 1, and proteinuria remission may be obtained either spontaneously or with immunosuppressive treatment.

Recurrence of anti-SEMA 3B-mediated MN after kidney transplantation was recently reported[34]. Kidney biopsy confirmed histological MN recurrence with the colocalization of SEMA 3B antigen and IgG. Treatment with rituximab was effective, and the disappearance of anti-SEMA 3B antibodies was noted 40 days after rituximab treatment.

Given the discovery of the antigen SEMA 3B, the distribution of podocyte antigens in patients with "primary" MN is presented in Figure 4.

Protocadherin 7-associated MN

Chauhan *et al*[35] performed laser microdissection and MS/MS in kidney biopsies from patients with PLA2R-negative MN and detected a unique protein, namely, protocadherin 7 (PCDH7) in glomeruli from 10 patients who were also negative for THSDF7A, EXT1/EXT2, NELL 1 and SEMA 3B. Additionally, in a validation cohort from the UCLouvain Kidney Disease Network in Belgium, four additional patients were identified[36]. In all patients, immunohistochemistry showed bright granular staining along the GBM. Confocal microscopy showed colocalization of PCDH7 and IgG along the GBM, and Western blot analysis using sera revealed antibodies against PCDH7.

Cadherins are a large group of transmembrane proteins that mediate cell-cell recognition and adhesion[37]. Cadherins are classified into subfamilies on the basis of the number and arrangement of extracellular cadherin (EC) domains. Therefore, cadherins are subdivided into classic cadherins, closely related cadherins, desmosomal cadherins and protocadherins[38]. PCDH7 is a 16-kDa glycosylated protocadherin with seven EC repeats. Its function is unknown, but it is likely important in cell signaling

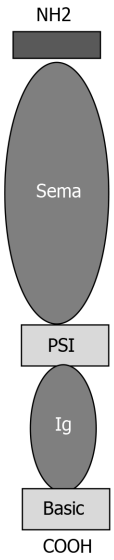

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Figure 3 Structure of Semaphorin. Sema: Sema domain; PSI: Plexin-semaphorin-integrin; Ig: Immunoglobulin.

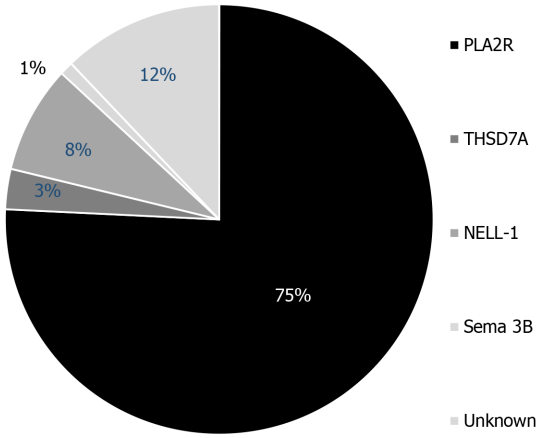

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Figure 4 Distribution of podocyte antigens in patients with 'primary' membranous nephropathy. PLA2R: Phospholipase A2 receptor; THSD7A: Thrombospondin type 1 domain containing 7A; NELL-1: Neural epidermal growth factor-like 1 protein; Sema: Sema domain.

[39]. PCDH7 is mostly present in older patients. Complement activation is minimal in these patients, and spontaneous remission frequently occurs without immunosuppressive treatment. In addition, the MS/MS complement profile of PCDH7-associated MN is lower than that of other antigen-associated MNs[40]. The clinical and pathologic findings in PCDH7-associated MN are described in Table 2.

In conclusion, PCDH7 has been identified as a novel antigen along with circulating anti- PCDH7 autoantibodies, in a subset of adult patients with PLA2R-negative MN.

Interestingly, Bobart *et al*[41] analyzed a total of 320 adult patients with MN in native kidneys between 2015 and 2020. Overall, they found three patients with PCDH7-associated MN. This study is interesting as the authors presented a patient distribution based on the antigen found and the presence of associated diseases (Figure 5). Similarly, the authors presented a table reporting the demographic and clinical characteristics based on the antigen involved (Table 3).

The new classification of MNs is shown in Figure 6.

Sethi[42] suggested that MN is not a single disease but rather a pattern of injury resulting from different diseases. Each antigen associated with the MN pattern should be considered as representative of a specific disease, and each disease results in an MN pattern of injury (Figure 7).

Newly discovered antigens

As described in Figure 6, other antigens and immune complexes are probably less frequently involved. Recently, Contactin 1 was shown to be a novel target antigen in MN associated with chronic inflammatory demyelinating polyneuropathy (CIDP)[43].

Table 2 Clinical and immunomicroscopy findings in protocadherin patients[35,36]

Patient	Age (yr)	Urinary protein (g/24h)	Serum creatinine (mg/dL)	Immunofluorescence	IgG
1	73	3.2	1.1	IgG 3+; C1q 1+	IgG1 2+; IgG3 1+; IgG4 1+
2	66	9.6	1.3	IgG 2+	IgG1 1+; IgG4 2+
3	68	NA	1.1	IgG 2+	IgG4 2+
4	59	3	1.1	IgG 2+; C3 1+	1gG 1+; IgG2 2+; IgG3 2+; IgG4 3+
5	61	7	1.9	IgG 3+; C3 1+	IgG1 2+; IgG3 2+
6	38	3	1	IgG 1+	NA
7	37	1.4	1.76	IgG3 +	IgG4 1+
8	67	4.3	1.2	IgG 3+	NA
9	75	7	1	IgG 3+; C3 1+	NA
10	70	1	1.6	IgG 3+; C3 1+	NA
11	64	8.4	1.2	IgG 3+; C3 3+	IgG3 2+; IgG2 2+
12	61	3.9	1	IgG 3+	IgG4 2+; IgG2 1+
13	66	23.3	3.8	IgG 3+; IgA 2+	IgG4 2+; IgG2 2+
14	72	21	1.3	IgG 1+	NA

NA: Not applicable. IgG: Immunoglobulin G; IgA: Immunoglobulin A.

Table 3 Demographic and clinical characteristics according to antigen

Total 270	PLA2R 220	EXT1/EXT2 11	NELL 1 6	PCDH7 3	THSD7A 1	NCAM-1 1	Septule negative 28
Age	54.0 (43.2-61.0)	40.0 (25.0-48.0)	57.0 (36.7-66.5)	73 (69.0-74.0)	67.0	46	52 (44.5-66.5)
Male sex % (*n*)	75.0 (165/220)	27.2 (3/11)	66.6 (4/6)	33.3 (1/3)	100 (1/1)	0 (0/1)	60.7 (17/28)
Serum creatinine (mg/dL)	1.1 (0.9-1.4)	1.0 (0.7-1.1)	1.9 (1.0-4.9)	1.1 (1.03-1.48)	0.9	0.6	1.2 (0.9-1.7)
eGFR (mL/min/1.73 m^2)	68 (49.9-91.0)	85.0 (65.2- 113.4)	38.3 (14.5-75.7)	57 (39.8-66.6)	89.5	114.0	67 (40.0-95.0)
Proteinuria (g/24 h)	8.0 (5.2-12.0)	5.6 2.6-9.3)	11.0 (6.8-16.1)	3.2 (1.55-6.05)	14.4	5.7	4.5 (3.2-9.9)
Malignancy %	5.0 (11/220)	9.0 (1/11)	33.3 (2/6)	-	100 (1/1)	-	25.0 (7/28)
Autoimmunity %	5.4 (12/220)	81.8 (9/11)	33.3 (2/6)	-	-	-	46.4 (13/28)
Paraproteinmemia %	4.0 (9/220)	-	-	-	100 (1/1)	-	35 (1/28)
Infection %	0.4 (1/220)	-	-	-	-	-	-
NSAID %	1.8 (4/220)	-	16.6 (1/6)	-	-	-	14.2 (6/28)
No associated disease %	84.0 (185/220)	18.1 (2/11)	16.6 (1/6)	100 (3/3)	-	100 (1/1)	21.4 (6/28)

eGFR: Estimated glomerular filtration rate; EXT: Exostosin; NCAM-1: Neural cell adhesion molecule 1; NELL-1: Neural epidermal growth factor-like 1 protein; NSAID: Nonsteroidal anti-inflammatory drug; PCDH7: Protocadherin; PLA2R: Phospholipase A2 receptor; THSD7A: Thrombospondin type 1 domain containing 7A.

In 2018, Hashimoto *et al*[44] described a patient with chronic inflammatory demyelinating polyneuropathy with concurrent MN. CIDP may be due to autoantibodies against paranodal proteins, such as neurofascin 155 (NF155) and contactin-1 (CNTN1).

Autoantibody assays revealed the presence of IgG4- and IgG1-reactive anti- CNTN1 in MN. The authors hypothesized that CIDP with MN, can be detected by anti-CNTN1 antibodies in some cases.

More recently, Xu *et al*[45] described a 57-year-old man admitted to the hospital for limb numbness, weakness and sensory disorder. This man had MN and was diagnosed with anti-CNTN1 antibody-associated autoimmune nodopathy. Reviewing the literature, the authors found 22 cases of CIDP with

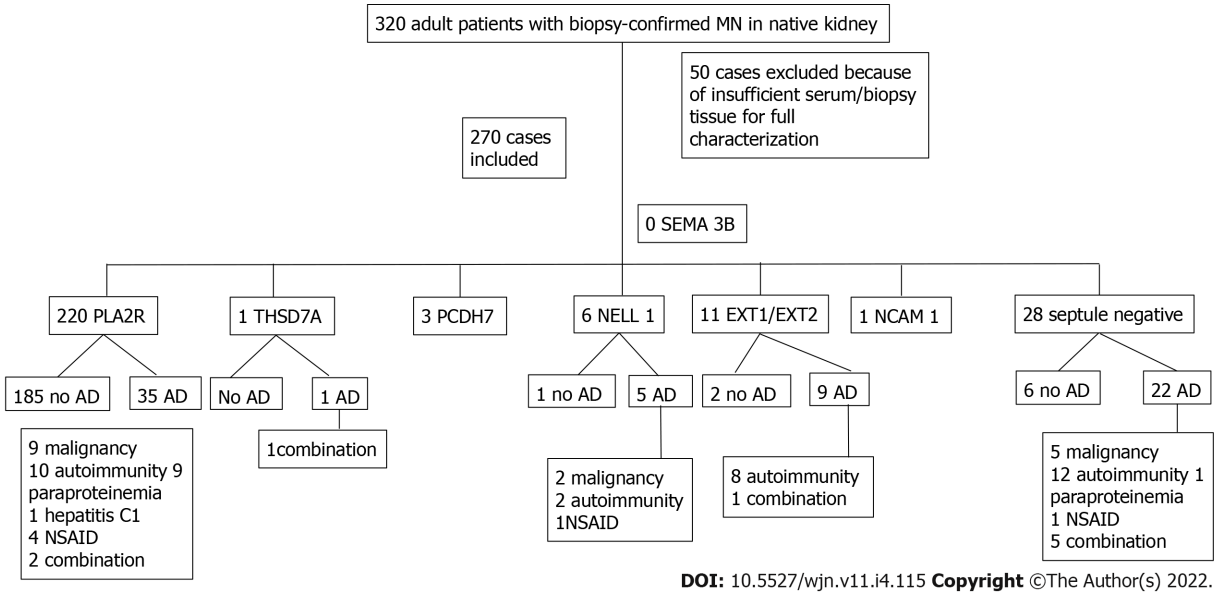


Figure 5 Patient distribution according to antigen and presence of associated disease. AD: Associated disease; NSAID: Nonsteroidal anti-inflammatory drug; EXT: Exostosin; MN: Membranous nephropathy; NCAM-1: Neural cell adhesion molecule 1; NELL-1: Neural epidermal growth factor like-1 protein; PCDH7: Protocadherin; PLA2R: Phospholipase A2 receptor; SEMA 3B: Semaphorin 3B; THSD7A: Thrombospondin type 1 domain containing 7A.

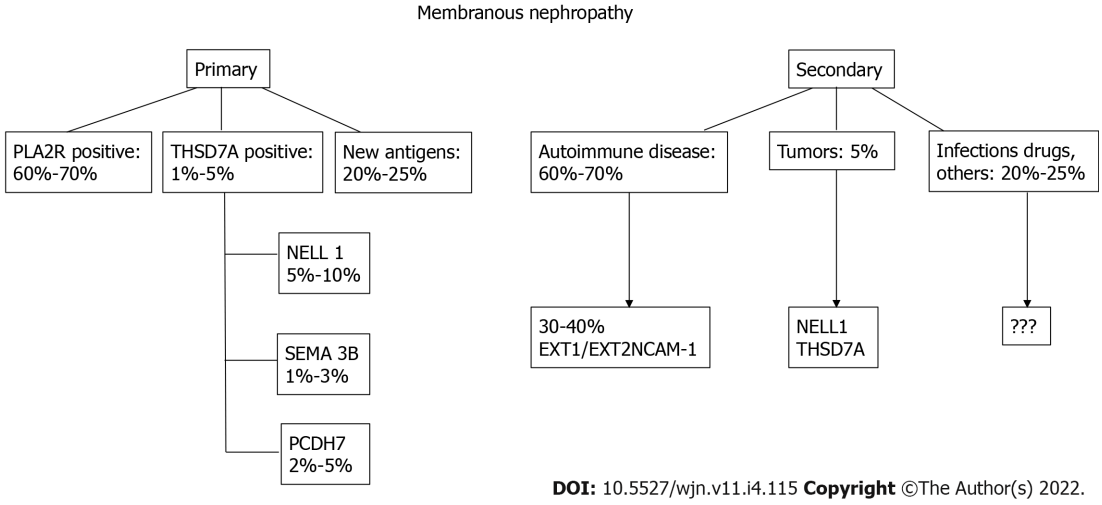


Figure 6 New proposed classification of membranous nephropathy. PLA2R: Phospholipase A2 receptor; THSD7A: Thrombospondin type 1 domain containing 7A; NELL-1: Neural epidermal growth factor-like 1 protein; Sema: Sema domain; PCDH7: Protocadherin 7; EXT: Exostosin; NCAM-1: Neural cell adhesion molecule 1.

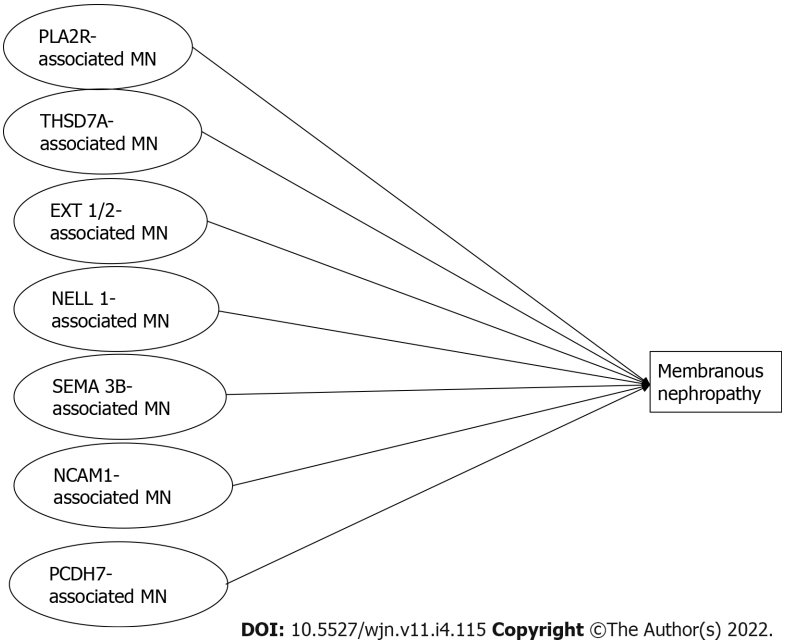
MN, five of which were associated with the anti-CNTN1 antibody[46-49]. However, given the limited available research, no conclusions regarding a common antigen can be drawn.

In their recent study, Le Quintrec *et al*[43] looked for a novel target antigen by analyzing kidney biopsies from 5 patients positive for anti-contactin 1 antibodies who presented with MN combined with chronic inflammatory demyelinating polyneuropathy.

Western blot analysis revealed contactin 1 expression in kidney glomeruli. Confocal microscopic analysis showed the presence and colocalization of contactin 1 and IgG4 on the GBM. Eluted IgG could bind paranodal tissue and colocalized with commercial anti-contactin 1 antibody. Based on these findings, contactin 1 is a novel common antigenic target in MN associated with chronic inflammatory demyelinating polyneuropathy.

CTNT 1 is a glycosylphosphatidylinositol-anchored cell membrane protein expressed on the extracellular side.

Anti-CNTN1 predominantly comprises the IgG4 subclass. IgG4 deposits were found to colocalize with CNTN 1 or PLA2R1 in kidney biopsies. IgG4-PLA2R1-MN is considered a kidney autoimmune disease. After the formation of immune complexes, complement may be activated[50].



DOI: 10.5527/wjn.v11.i4.115

Figure 7 Schematic classification of different conditions leading to membranous nephropathy. PLA2R: Phospholipase A2 receptor; THSD7A: Thrombospondin type 1 domain containing 7A; NELL-1: Neural epidermal growth factor-like 1 protein; Sema: Sema domain; PCDH7: Protocadherin 7; EXT: Exostosin; NCAM-1: Neural cell adhesion molecule 1; MN: Membranous nephropathy.

In conclusion, CNTN1 is the first discovered target involved in combined MN and anti-CNTN1-related CIDP.

Le Quintrec *et al*[43] detected three proteins (CNTN1, CASPR1, and NF155) in human glomerular extracts by immunoblotting and mass spectrometry. The authors were unable to show CNTN1 staining in podocytes in the normal human kidney. This finding could be ascribed to the fact that epitopes recognized by anti-CNTN1 antibodies are accessible only under pathological conditions[51].

CONCLUSIONS

MN has long been classified as primary MN (70%) with no disease association, and secondary MN (30%) with an underlying disease such as autoimmune disorders, tumors or infections. The principal known antigens involved as targets in primary MN were phospholipase A2 receptor and THSD7A. The availability of new techniques has allowed the discovery of new antigens and antibodies that are less frequently involved. Preliminary studies of patients at follow-up have shown different pathological findings and different outcomes associated with each of these new antigens. Now, it is possible that each new-type of antigen associated MN represents a distinct disease that causes the deposition of immune deposits along the GBM. The thickening of the GBM is the common result of these different diseases.

FOOTNOTES

Author contributions: Salvadori M and Tsalouchos A contributed equally to the manuscript; Salvadori M designed the study, performed the last revision and provided answers to the reviewers; Tsalouchos A collected the data from literature; Salvadori M and Tsalouchos A analyzed the collected data and wrote the manuscript.

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Country/Territory of origin: Italy

ORCID number: Maurizio Salvadori 0000-0003-1503-2681; Aris Tsalouchos 0000-0002-8565-4059.

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Observational Study

Concordance between bio-impedance analysis and clinical score in fluid-status assessment of maintenance haemodialysis patients: A single centre experience

Kamiti Muchiri, Joshua K Kayima, Elijah N Ogola, Seth McLigeyo, Sally W Ndung'u, Samuel K Kabinga

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Kamiti Muchiri, Joshua K Kayima, Seth McLigeyo, Clinical Medicine and Therapeutics, University of Nairobi, Nairobi +254, Kenya

Elijah N Ogola, Department of Clinical Medicine and Therapeutics, University of Nairobi, Nairobi +254, Kenya

Sally W Ndung'u, Department of Public Health, University of Nairobi, Nairobi +254, Kenya

Samuel K Kabinga, East African Kidney Institute, University of Nairobi, Nairobi +254, Kenya

Corresponding author: Samuel K Kabinga, MBChB, MD, Doctor, East African Kidney Institute, University of Nairobi, P.O. Box 30197, Nairobi +254, Kenya. kabingas@yahoo.com

Abstract

BACKGROUND

The burden of chronic kidney disease (CKD) is rising rapidly globally. Fluid overload (FO), an independent predictor of mortality in CKD, should be accurately assessed to guide estimation of the volume of fluid to be removed during haemodialysis (HD). Clinical score (CS) and bio-impedance analysis (BIA) have been utilized in assessment of FO and BIA has demonstrated reproducibility and accuracy in determination of fluid status in patients on HD. There is need to determine the performance of locally-developed CSs in fluid status assessment when evaluated against BIA.

AIM

To assess the hydration status of patients on maintenance HD using BIA and a CS, as well as to evaluate the performance of that CS against BIA in fluid status assessment.

METHODS

This was a single-centre, hospital-based cross-sectional study which recruited adult patients with CKD who were on maintenance HD at Kenyatta National Hospital. The patients were aged 18 years and above and had been on maintenance HD for at least 3 mo. Those with pacemakers, metallic implants, or bilateral limbs amputations were excluded. Data on the patients' clinical history, physical examination, and chest radiograph findings were collected. BIA was

performed on each of the study participants using the Quantum® II bio-impedance analyser manufactured by RJL Systems together with the BC 4® software. In evaluating the performance of the CS, BIA was considered as the gold standard test. A 2-by-2 table of the participants' fluid status at each of the CS values obtained compared to their paired BIA results was constructed (either ++, +-, -- or -+ for FO using the CS and BIA, respectively). The results from this 2-by-2 table were used to compute the sensitivity and specificity of the CS at the various reference points and subsequently plot a receiver operating characteristic (ROC) curve that was used to determine the best cut-off point. Those above and below the best CS cut-off point as determined by the ROC were classified as being positive and negative for FO, respectively. The proportions of participants diagnosed with FO by the CS and BIA, respectively, were computed and summarized in a 2-by-2 contingency table for comparison. McNemar's chi-squared test was used to assess any statistically significant difference in proportions of patients diagnosed as having FO by CS and BIA. Logistic regression analysis was conducted to assess whether the variables for the duration of dialysis, the number of missed dialysis sessions, advisement by health care professional on fluid or salt intake, actual fluid intake, the number of anti-hypertensives used, or body mass index were associated with a patient's odds of having FO as diagnosed by BIA.

RESULTS

From 100 patients on maintenance HD screened for eligibility, 80 were recruited into this study. Seventy-one (88.75%) patients were fluid overloaded when evaluated using BIA with mean extracellular volume of 3.02 ± 1.79 L as opposed to the forty-seven (58.25%) patients who had FO when evaluated using the CS. The difference was significant, with a *P* value of < 0.0001 (95% confidence interval: 0.1758-0.4242). Using CS, values above 4 were indicative of FO while values less than or equal to 4 denoted the best cut-off for no FO. The sensitivity and specificity for the CS were 63% and 78% respectively. None of the factors evaluated for association with FO showed statistical significance on the multivariable logistic regression model.

CONCLUSION

FO is very prevalent in patients on chronic HD at the Kenyatta National Hospital. CS detects FO less frequently when compared with BIA. The sensitivity and specificity for the CS were 63% and 78% respectively. None of the factors evaluated for association with FO showed statistical significance on the multivariable logistic regression model.

Key Words: Bio-impedance analysis; Clinical score; Chronic kidney disease; Maintenance haemodialysis; Fluid overload; Concordance

Core Tip: Bio-impedance analysis (BIA) has been validated as an accurate and reliable tool for determining fluid status in chronic kidney disease (CKD) patients but is not widely available in low-income settings. In this study we assess how a clinical score (CS) compares with BIA in this population for possible use as a low-cost substitute where BIA is not available. Patients with a CS score greater than 4 were considered to have fluid overload (FO), and detected using this parameter in 58.75% of patients. CSs of ≤ 4 represented no FO, and represented 41.25% of patients. The CS had a sensitivity of 63% and a specificity of 78% in making a diagnosis of FO compared with BIA, which was used as the reference in patients with CKD on maintenance haemodialysis.

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INTRODUCTION

Chronic kidney disease (CKD) refers to the abnormalities in kidney structure and function with effects on the individual's health for more than 3 mo. The indicators for kidney damage include reduced estimated glomerular filtration rate, abnormal urinalysis findings, or abnormal histologic findings on kidney biopsy[1]. The risk factors for CKD include diabetes mellitus (DM), high blood pressure, and

glomerulonephritides[2,3]. Advanced CKD is heralded by general ill-health, symptomatic anaemia, signs and symptoms of uraemia, and fluid overload (FO). End stage kidney disease (ESKD) is characterised by reduced ability to excrete enough sodium and the resultant water retention, which presents as a FO state. In this state, the patient requires kidney replacement therapy (KRT) for sustenance of bodily functions. The KRT modalities include dialysis and kidney allograft transplantation. Dialytic modalities include haemodialysis (HD) and peritoneal dialysis (PD). In Africa, less than 3% of those who require KRT receive it, with HD as the most popular modality[4].

Fluid status

The extracellular volume (ECV) varies by ± 1 L in healthy individuals and is dependent on salt intake. The ECV is severely affected by kidney disease. FO is defined as the ECV in excess of that observed in healthy individuals with normal kidney function[5]. Chronic FO increases mortality from arterial hypertension, left ventricular dilatation and hypertrophy, and congestive heart failure[6]. Oedema predisposes the patient to skin infections, especially in diabetic patients, and can result in sepsis, limb amputations, and high mortality. Oedema in the gut leads to malabsorption of nutrients and, in the lungs, it increases risk of bronchitis and pneumonia[7]. Among the patients with CKD, the state of hydration comes only second to the presence of DM in predicting mortality[8]. Greater than 15% of relative overhydration corresponds to > 2.5 L FO and is independently associated with high mortality [9]. This degree of over hydration is associated with an 8.5% increase in deaths even in stable CKD group of patients on dialysis[8]. HD removes waste products and fluids. Conversely, dehydration is associated with muscular cramps, low blood pressure, cardiac stunning, and loss of residual kidney function[6].

Several methods have been employed in assessment of fluid status in CKD patients. Varied signs and symptoms have been put together to comprise a clinical scoring system for assessment of state of hydration among patients. Clinical scores (CSs) are easy to document and can be recorded consistently and regularly. These make the scores appealing for utilization in assessment of hydration status. However, clinical scoring systems have inherent weaknesses of incompleteness, subjectivity of the observer, and lack of specificity. The specificity of CSs can be increased by scoring symptoms that manifest *de novo* and clear with correction of hydration status. Wizemann *et al*[10] utilized this approach in a study whereby signs and symptoms of dehydration and FO were grouped and scored.

There are other methods which have been employed in assessment of the fluid status. These include imaging like chest X-rays and ultrasonographic scanning, monitoring of plasma volume by dilution methods, clinical methods, and bio-impedance analysis (BIA). The BIA is based on the principle that in a cylinder, the electrical impedance varies directly with length and inversely to the product of cross-sectional area and specific sensitivity[9]. In BIA, an alternating current is passed through the body and the current passes extra- or intracellularly depending on whether it is low or high. High frequency current passes through extra- and intracellular spaces. Bio-impedance-defined overhydration (OH) independently predicts mortality due to its ability to discriminate absolute and relative extracellular fluid (ECF) volume[9].

Employment of various techniques simultaneously can achieve better results in evaluation of hydration status in patients. However, this is not practically feasible in a clinical setting. We hypothesised that the CS and BIA were equal in assessing hydration status of adult patients on maintenance HD. This study assessed the hydration status of patients on maintenance HD using BIA and CS in addition to determining of degree of concordance between the two methods in assessment of hydration status. The study determined the factors associated with FO in this population, which included the HD vintage, knowledge and practice of fluid and salt restrictions, the number of antihypertensive or diuretic medications, and body mass index (BMI). Approval was obtained from the Kenyatta National Hospital - University of Nairobi Ethics and Research Committee under proposal P822/012/2018.

MATERIALS AND METHODS

This was a single-centre hospital-based cross-sectional analytic study carried out between March and April 2019. It was performed in the Renal Department at the Kenyatta National Hospital, which is a national teaching and referral hospital located in Nairobi-Kenya. The study recruited ESKD who had been on maintenance HD. Those included were adult patients aged ≥ 18 years who had been on HD for at least 3 mo. We excluded patients who had undergone bilateral limbs amputation, had implanted metallic devices, pacemakers, or metallic intravascular devices, or who were very sick.

The sample size was estimated using the sample size formula for comparing paired proportions (McNemar's *Z* test, 2-sided equality)[11]. Using the prevalence of FO using BIA by Bajaber *et al*[12] (69%), prevalence of FO using a CS by Wizemann *et al*[10] (35%), α of 5% and β of 20%, the calculated sample size after adjusting upwards by 15% to account for non-response was 80 patients. The study employed systematic random sampling without replacement. Structured history and physical examinations were performed by one clinician. Weight was measured to the nearest 0.1 kg using a digital scale placed on a firm flat surface after the participants had removed heavy outer garments, shoes and

emptied their pockets. The weighing scale was calibrated daily. The height was taken using a stadiometer and employed a standard protocol. Two measurements were taken and the average of the two readings recorded to the nearest centimetre. Oedema was assessed using a standard scoring system for uniformity[13].

Chest radiographs were obtained to assess findings of FO. The findings assessed included dilated veins in the upper lung zones and cardiomegaly that were classified as stage 1 hypervolemia. Stage 2 hypervolemia was marked by interstitial oedema evidenced by Kerley B lines, while stage 3 was evidenced by alveolar oedema or pleural effusion as reported by two radiologists at the University of Nairobi who were blinded to study procedures. A CS that had not been previously validated was developed for the study. It entailed eliciting signs and symptoms for hypovolemia like intradialytic hypotension, muscle cramps, dizziness, or fatigue during HD session and the need for treatment of hypotension with normal saline infusion, which were scored at -1 each. Signs and symptoms scored as hypervolemia included hypertension, hypoxia noted by oxygen saturation < 90%, presence of ascites, pleural effusion, or pulmonary oedema, which were scored at +1 each. The interdialytic weight gain was determined and scored as +1 for each kilogram gained since the last session of HD. Presence of gallop rhythm was scored at +2, dyspnoea classification by New York Heart Association was scored from 0 to +3, chest radiograph features of FO scored from +1 to +3 based on stages described above, and oedema of ankles and tibia was scored from 0 to +4 as shown in Table 1.

BIA was done by placing electrodes on one side of the body either left or right upper and lower limbs after lying supine for 10 min. For patients who used arteriovenous fistulae (AVF) for HD vascular access, the side without AVF was used. Measurement of resistance and reactance were then determined based on the manufacturer's guidelines. The machine used was the Quantum® II bio-impedance analyser manufactured by RJL Systems, Inc., Clinton Township, Michigan, United States, together with the BC 4® software from the same manufacturer. Hydration status was based on Wabel *et al*[14], which classified fluid status into three categories based on ECF estimation by BIA. These included dehydration where the ECF is estimated to be less than of -1.1 L, normal hydration with ECF ± 1.1 L, and FO where ECF is > 1.1 L. FO was further stratified as mild FO, where ECF was 1.1-2.5 L, and gross FO, where ECF was > 2.5 L.

The target variable was FO, as diagnosed by the newly developed CS and BIA. The predictor variables included BMI in kg/m^2, blood pressure in mmHg, antihypertensive medications used, fluid intake, salt intake, number of HD sessions per week, adherence to HD treatment, missed HD sessions during the 2 wk preceding the study period, HD vintage, antihypertensive medications, and fluid restriction. An adherent patient was one who had not missed any HD sessions in the 2 wk that preceded the study or any doses of scheduled antihypertensive medications in the week prior to evaluation and had received education on fluid and salt restriction which the patient was following, all based on the patients' self-report.

Statistical analysis

Data were analysed using STATA® software. Continuous variables included age, duration of CKD, HD vintage, systolic and diastolic blood pressure, and BMI. Normally distributed continuous data had their means and standard deviations computed. For skewed continuous data, medians and inter-quartile ranges (IQR) were computed. Categorical variables like sex, co-morbidities, hydration status by both CS and BIA, and HD vascular access, had frequencies calculated and were presented as counts and percentages. The result for each participant's CS (positive or negative for FO) was compared to its paired BIA result. Using BIA as the gold standard test for diagnosing FO, the CS sensitivity and specificity measures together with the false positive rate (FPR) at each of the CS values obtained by the participants were computed using the formulae: Se = TP/(TP + FN), Sp = FP/(FP + TN), FPR = 1 – SP. Where Se was sensitivity, Sp was specificity, TP was true positive, FN was false negative, FP was false positive, TN was true negative.

A receiver operating characteristic (ROC) curve (graph of sensitivity *vs* FPR) was plotted for scores obtained in order to establish the best cut-off point for determining FO using the CS[15]. The point which gave the greatest area under the ROC and in which the differential positive rate (DPR) value was highest was interpreted as the optimal cut-off point for the CS. The DPR was calculated using the formula: DPR = (Se + Sp) – 1. Values of the CS that were above and below the cut-off point were established as optimal on the ROC were interpreted as positive and negative for FO respectively.

The McNemar's chi square test was used to assess any statistically significant differences in proportions of patients diagnosed as having FO by both CS and BIA. Stepwise logistic regression analysis was conducted in order to assess whether the duration of dialysis, number of missed dialysis sessions, advise on fluid intake, actual fluid intake, advise on salt intake, number of anti-hypertensives used, and BMI were significant predictors of FO in this study population. Univariable logistic regression models between each of the predictor variables and FO was conducted at a liberal *P* value of 0.20. The variables having a *P* value of < 0.20 in the univariable models were added to the multivariable model where their association with the odds of FO was tested at a 5% significance level. Non-significant variables were eliminated from the multivariable model if they did not result in > 30% change in the coefficient of the significant variables[16]. The Hosmer-Lemeshow goodness of fit was computed to evaluate how well the final logistic regression model fit the data with a *P* value > 0.05, indicating a well-

Table 1 Clinical score parameters

Symptoms		Score
Scored as dehydration	Intradialytic hypotension	-1
	Muscle cramps, dizziness or fatigue during current session of dialysis	-1
	Symptomatic dialysis hypotension treated by NaCl (0.9%) infusion	-1
Scored as normohydration	Absence of symptoms given in this table	0
Scored as fluid overload	Hypertension	+1
	SPO_2 less than 90%	+1
	Presence of ascites	+1
	Presence of pleural effusion or pulmonary oedema on clinical examination	+1
	Inter dialytic weight gain - per 1 kg gained	+1
	Presence of gallop rhythm	+2
	Dyspnoea based on NYHA class	0 to +3
	Chest radiography features based on stage	+1 to +3
	Oedema (ankles, tibial, graded)	0 to +4

NaCl: Sodium chloride; NYHA: New York Heart Association; SPO_2: Oxygen saturation.

fitting model[15].

RESULTS

Demographic and clinical profiles of study participants

Altogether, there were about 100 patients who were on maintenance HD at Kenyatta National Hospital renal unit between March and April 2019. All 100 patients were screened for eligibility. Eleven patients were excluded because they had been on HD for less than 3 mo, two had metallic implants, two declined to participate, two were below 18 years of age, and one patient was critically ill. The excluded patients were aged between 15 years and 70 years with a median age of 40 years and were predominantly male (60%). Eighty-two patients met the inclusion criteria and were recruited into the study. However, at the time of analysis, it was noted that two participants had incomplete data (missing chest radiographs) and were excluded from the final analysis. The two excluded were a male and female patient, aged 53 years and 27 years, on HD for 28 and 3 mo, respectively. By BIA, their hydration statuses were normohydrated and gross OH, respectively. The final analyses included 80 participants (Figure 1).

Table 2 summarizes demographic and clinical characteristics of the study participants. The study participants were aged between 18 years and 75 years with a median age of 45 years with an IQR of 20.5 years. Forty-six (57.5%) were males. Most (63.75%) of the patients had secondary level education or higher. Fifty-seven (71.25%) of the participants were married and the majority (93.75%) had medical insurance that covered the costs of their HD, for a maximum of two HD sessions per week.

The median duration since diagnosis of CKD was 12.5 mo (IQR 24.5) and the median dialysis duration was 9 mo (IQR 15). Twenty-six (32.5%) patients had AVF while 54 (67.5%) were using venous catheters for HD vascular access. Seventy-seven (96.25%) patients had some residual kidney function while three participants were anuric. The comorbidities that preceded CKD as per their medical records included hypertension in 41 (51.25%) patients, glomerulonephritis in 22 (27.5%) patients, DM in 14 (17.5%) patients, obstructive uropathy in 8 (10%) patients, human immunodeficiency virus infection in 7 (8.75%) patients, kidney allograft failure in 2 (2.5%) patients, and cystic kidney disease in 1 (1.25%) patient. Seventy-six (95%) patients attended HD sessions twice per week as per institutional protocol with one of the patients on daily dialysis because he was scheduled for a kidney allograft transplantation during the week of assessment. Three (3.75%) patients were on once weekly HD. Sixty-six (82.5%) patients reported full adherence to attendance of their HD sessions and had not missed any sessions in the 2 wk preceding the study. Seventy-two (90%) patients had received education on fluid intake with the average actual fluid intake being 1010 mL in the interdialytic period with a range of 200-2800 mL. Seventy (87.5%) patients had received education on salt intake.

Table 2 Demographic and clinical characteristics of study participants

Characteristic		Statistic
Age (yr)	Median (IQR)	45 (20.5)
Sex	Male, *n* (%)	46 (57.5)
CKD duration (mo)	Median (IQR)	12.5 (24.5)
Dialysis vintage	Median (IQR)	9 (15)
Blood pressure (mmHg)	Systolic mean ± SD	150 ± 31
	Diastolic mean ± SD	91 ± 19
Body mass index (kg/m^2)	Median (IQR)	21.94 (5.13)
Comorbidities	Hypertension, *n* (%)	41 (51.25)
	Glomerulonephritis, *n* (%)	22 (27.5)
	Diabetes mellitus, *n* (%)	14 (17.5)
	Obstructive uropathy, *n* (%)	8 (10)
	HIV, *n* (%)	7 (8.75)
	Malignancy, *n* (%)	2 (2.5)
	Graft failure post-transplant, *n* (%)	2 (2.5)
	Cystic kidney disease, *n* (%)	1 (1.25)
Dialysis access	Arterio-venous fistula, *n* (%)	26 (32.5)
Clinical score	Hypovolemia, *n* (%)	0 (0.00)
	Normovolemia, *n* (%)	33 (41.25)
	Hypervolemia, *n* (%)	47 (58.25)
BIA	Dehydration, *n* (%)	0 (0.00)
	Normal hydration, *n* (%)	9 (11.25)
	Fluid overload, *n* (%)	71 (88.75)
	Mild FO, *n* (%)	25 (31.25)
	Gross FO, *n* (%)	46 (57.50)

BIA: Bio-impedance analysis; CKD: Chronic kidney disease; FO: Fluid overload; HIV: Human immunodeficiency virus; IQR: Interquartile range.

Fifty (62.5%) of the patients had systolic blood pressure (SBP) > 140 mmHg with mean SBP of 150 ± 31 mmHg. The mean diastolic blood pressure (DBP) was 91 ± 19 mmHg with 41 (51.25%) patients having DBP > 90 mmHg. Four patients (5%) were hypotensive with either SBP less than 90 mmHg or DBP less than 60 mmHg. Forty-four (55%) patients were on two or three antihypertensive agents. The median BMI was 21.94 kg/m^2 (19.50-25.63). Seventy (87.5%) patients had received health education on salt intake as part of their management prior to enrolment on the study. Sixty-seven (83.75%) patients self-reported strict adherence to their anti-hypertensive medications and had not missed any of the prescribed dose in the week prior to evaluation. Forty-eight (60%) patients reported complete adherence to all the specific aspects ESKD management, which this study sought. The patients had received all the prescribed number of HD sessions in the previous 2 wk and had adhered to dietary, salt, and fluid intake restrictions, as well as having not skipped any of the prescribed doses of anti-hypertensive medications in the week that preceded this study.

Volume status as determined by BIA

The participants had volumes in the range of -0.53 L to 8.23 L and a median of 2.76 L (IQR 2.22 L). Fluid overload was found in 71 (88.75%) patients of which 46 (57.50%) were grossly overloaded with ECV of 2.5 L above the normal volume. Nine (11.25%) patients had normal volume, and none were dehydrated according to evaluation by BIA. On average, the study participants had 3.02 ± 1.79 L of ECV.

Volume status as determined by CS

Symptoms scored as dehydration were scored in the negative. There were 2 (2.5%) with intradialytic hypotension, 1 (1.25%) with muscle cramps, dizziness, or fatigue during current session of dialysis, and

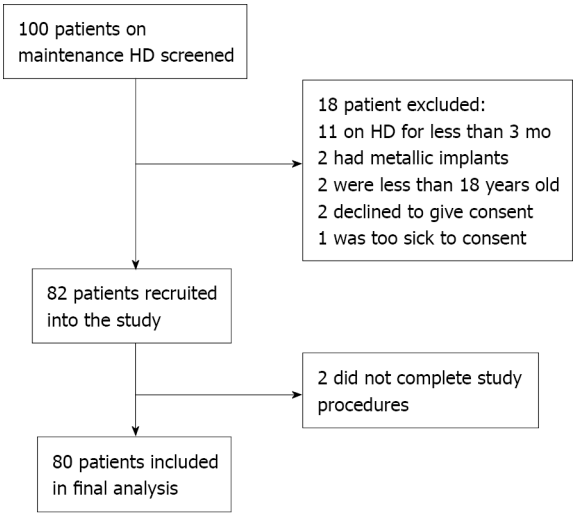

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Figure 1 Study flow diagram for screening and recruitment. HD: Haemodialysis.

1 (1.25%) with symptomatic intradialytic hypotension treated by normal saline infusion. Absence of the above symptoms were scored as normohydration at zero score. Signs and symptoms of FO scored from +1 to +4. There were 54 (67.5%) with hypertension, 8 (10%) with oxygen saturation less than 90% by digital pulse oximeter, 26 (32.5%) with ascites, and 15 (18.75%) with pleural effusion or pulmonary oedema, each scored at +1. Interdialtyic weight gain was scored at +1 per kilogram gained. Five (6.25%) of the patients had gallop rhythm, which was scored at +2. Dyspnoea was scored using New York Heart Association classification with 54 (67.5%) patients at class I, scored at zero, 17 (21.25%) at class II scored at +1, 9 (11.25%) at class III scored at +2, while none were at class IV, which would have scored at +3. Chest radiography features were scored between +1 and +3 based on the stages. Oedema was graded and scored between 0 and +4. CSs obtained varied from -2 to 16 with a mean of 5.46 ± 3.68. Each of the results obtained from the CS was used to generate sensitivity and FPR that were used to plot a ROC curve. As shown in Figure 2, the optimal cut-off point for the CS obtained from the ROC was 4. This gave the score 63% and 78% sensitivity and specificity respectively. At this cut-off point, fluid overload was picked in 58.75% while no overload was in 41.25% of the patients.

Level of agreement between BIA and CS

BIA showed that 9 (11.25%) of the patients had normal hydration, 71 (88.75%) were fluid overloaded, and none was dehydrated. The CS showed that 33 (41.25%) had normal hydration, 47 (58.25%) were fluid overloaded, and none was dehydrated (Table 2). Fifty-two (65%) patients had similar results by both BIA and CS, and consisted of 45 patients with FO and 7 patients without FO. Twenty-eight (35%) patients had differing results by the 2 methods. Bio-impedance diagnosed 26 patients to have FO, but these same patients were not picked by CS as having FO. CS picked two patients as having FO who were picked by BIA as not having FO. The calculated McNemar's chi-squared was 20.57 ($P < 0.0001$, 95% confidence interval: 0.1758-0.4242). The BIA detected significantly more patients with FO than CS. The true difference of the percentage of patients on HD picked with FO by CS and BIA was 17.58%-42.42% (Table 3).

Factors associated with FO

Duration of HD, number of missed HD sessions, whether the advice on fluid and salt restrictions against the fluid and salt was taken by the patient, as well as the number of antihypertensives medications each patient was using, and BMI were assessed for association with FO. Univariable logistic regression model of these factors associated with FO status was assessed. Using a liberal P value of 0.20, HD vintage in months, BMI and fluid intake were significantly associated with FO diagnosed by BIA (Table 4). However, from the multivariable model, using a significance level of 0.05, all these factors were not significantly associated with FO (Table 5).

DISCUSSION

The majority of the patients in this study were relatively young with a mean age of 45.6 years when compared with studies done in Europe, where the mean age was greater than 60 years[17]. The median duration of CKD was about 1 year and the median HD vintage was less than 1 year. There was a slight

Table 3 2-by-2 table assessing association between bio-impedance analysis and the clinical score

		Positive	Negative	Total	*P* value	95%CI
Clinical score	Positive	45	2	47		
	Negative	26	7	33		
	Total	71	9	80		
McNemar's Chi Square (20.57)					< 0.0001	0.1758-0.4242

CI: Confidence interval.

Table 4 Univariable analysis of factors associated with fluid overload

Variable	Values	FO+ (*n* = 71)	FO- (*n* = 9)	OR	95%CI	*P* value
Duration of dialysis[1] (mo)	3-76	71	9	1.05	0.967-1.147	0.13
No of missed dialysis sessions	0	59	7			
	≥ 1	12	2	0.712	0.131-3.856	0.70
Advised on fluid restriction	No	6	2			
	Yes	65	7	3.095	0.522-18.357	0.25
Actual fluid intake[1] (mL)	200-2800	71	9	0.998	0.997-1.000	0.082
Advised on salt intake	No	9	1			
	Yes	62	8	0.8611	0.096-7.719	0.89
Number of anti-hypertensives used	0	11	0			
	1	13	2			
	2	23	3			
	3	14	4			
	4	7	0			
	5	2	0			
	6	1	0	0.903	0.537-1.517	0.70
Patient's BMI[1] (kg/m^2)	15.82-32.53	71	9	1.196	0.942-1.520	0.11

[1]Variables eligible for inclusion in the multivariable model at a liberal *P* value of 0.20.
BMI: Body mass index; CI: Confidence interval; FO+: Positive fluid overload; FO-: Negative fluid overload; OR: Odds ratio.

Table 5 Multivariable analysis of factors associated with fluid overload

Variable	Values	OR	95%CI	*P* value
Duration of dialysis (mo)	3-76	1.054	0.962-1.154	0.258[a]
Actual fluid intake (mL)	200-2800	0.999	0.997-1.000	0.099[a]
BMI (kg/m^2)	15.82-32.53	1.191	0.934-1.519	0.159[a]

[a]*P* values are non-significant.
BMI: Body mass index; CI: Confidence interval; OR: Odds ratio.

male predominance. In a study performed elsewhere in Kenya[12], the age distribution, male predominance, and BMI were comparable to those of our study. The majority of the patients in this study also suffered from hypertension (67.5%). One of the contributors to sustained hypertension in this population is likely to be FO. The majority of the patients reported to have been counselled on diet and fluid and salt intake as a way of controlling blood pressure and FO, and they reported adherence to the recommendations. Educating patients on dietary salt and fluid restrictions are important components of

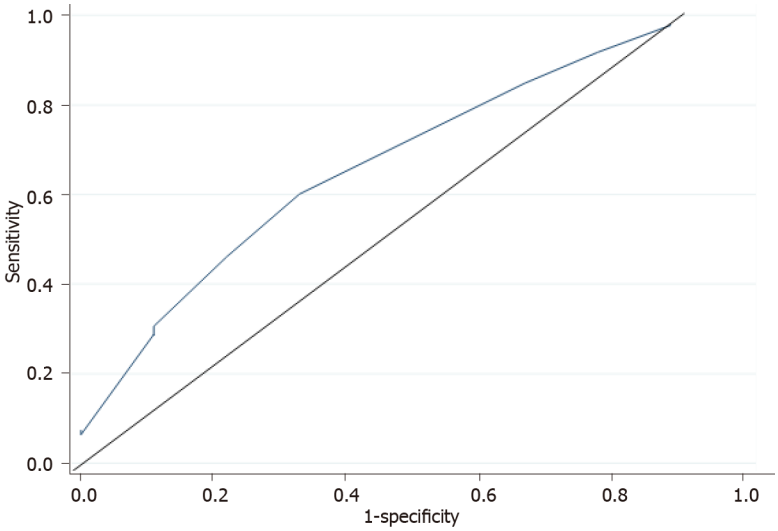

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Figure 2 Receiver operating characteristic curve for the clinical score.

the management of ESKD. Previous studies have shown that patients who fail to adhere to dietary salt and fluid intake restrictions are more likely to have FO[18]. Less than a fifth of the patients suffered from DM (17.5%). This is a lower proportion than that reported in other parts of the world, where prevalence rates of 29.7%[19] and as high as 50%[17] have been reported in some studies in Europe.

Almost all the patients (95%) were receiving 4-h HD sessions twice a week as per the Kenyatta National Hospital Renal Department protocol, partially because the health insurance could only reimburse two HD sessions per week and the patients could not afford to pay for an extra sessions out of pocket. This treatment frequency is less than the recommended thrice weekly[20]. The longer interdialytic period could lead to fluid accumulation and may contribute to the higher proportion of FO in our population. Assessment of fluid status by CS and BIA revealed that the majority of the patients were fluid overloaded. Slightly more than a half of the patients were fluid overloaded when accessed by CS while almost 90% of them were fluid overloaded when assessed by BIA. The BIA was more sensitive in picking FO status. More patients were noted to be fluid overloaded in this study compared to studies done elsewhere in South Africa and Europe[17,21,22]. A study from South Africa among patients on dialysis reported almost two in every three patients as being fluid overloaded[21]. In Germany, Passauer *et al*[17] reported similar proportion of patients on dialysis as being fluid overloaded. Almost 60% of patients in this study had more than 2.5 L of excess ECV; this is in contrast to an analysis of 1500 European HD patients of whom only 25% had gross FO[22]. A plausible explanation why studies done elsewhere have reported lower proportions of FO could be due to the fact that elsewhere, patients have HD sessions more than twice per week. The longer interdialytic period could result in more interdialytic fluid accumulation.

The proportion of patients with FO in our study was higher than that reported in a study at Moi Teaching and Referral Hospital in Kenya, where 7 in every 10 patients were reported to have FO[12]. This study excluded patients who had not attained dry weight, and this could explain why the proportion with FO was lower than that in our study. The study assessed the level of agreement between the FO status diagnosed by CS and by BIA. The difference between the numbers of patients picked as having FO by the two methods was significant. BIA was more sensitive in detecting FO when compared with CS. Similar observations had been made by Kalainy *et al*[23], and were attributed to an inherent low sensitivity and specificity of clinical parameters in picking the fluid volume before dialysis. In contrast, Wizemann *et al*[10] reported a better concordance between symptom score and BIA, with more agreement towards over hydration than dehydration. Vasko *et al*[24] compared BIA with history, signs and symptoms, laboratory evaluation, and routine imaging with chest X-rays, lung ultrasound scanning, and cardiac evaluation with echocardiograph. They concluded that clinical judgment was the most important in assessing pre-dialysis OH. Use of patient history and examination, as well as chest radiograph data, compared favourably with BIA in guiding clinical decisions. At a cut-off point of 4, the CS resulted in 63% and 78% sensitivity and specificity respectively. The BIA was more sensitive in picking patients with FO than CS and the true difference of the percentage of patients on HD picked with FO by CS and BIA was 17.58%-42.42%.

Our study was limited by the small sample size and being done in a single centre. Some tests, which could aid in assessing FO, like echocardiography, were not performed in our study population due to financial constraints. The study relied on the recall by the patients and was subject to recall bias, especially on adherence to diet and fluid intake. Some aspects, which were purely self-reported by the patients, were not verifiable.

CONCLUSION

FO is very prevalent in patients on chronic HD at the Kenyatta National Hospital. CS picks less FO when compared with BIA. However, CS could still pick more than 6 in 10 patients with FO as picked by BIA with a specificity of almost 80%. In settings where BIA is not available, CS can be utilized as a low-cost alternative to assess fluid status of patients on HD and interpreted with the knowledge that CS identifies fewer patients with FO than does BIA.

Use of BIA should be incorporated into the routine care of patients on maintenance HD. CS should also be utilized in assessment of FO, especially in places where BIA is not available. Further studies are needed to evaluate how CS compares with BIA in bigger and heterogeneous populations. It is plausible to try and increase the HD sessions to thrice per week in attempt to reduce the proportion of patients who present with FO in our setting. In addition, future studies can evaluate the validity of the CS where patients have attained their dry weight at the baseline since this may improve both the sensitivity and the specificity.

ARTICLE HIGHLIGHTS

Research background

Assessment of fluid status in patients with chronic kidney disease (CKD) on haemodialysis (HD) is important to guide treatment. Objective methods of assessment fluid status in this population of patients are needed. In CKD patients on HD, bio-impedance analysis (BIA) is reliable in assessment of fluid status though not available in many clinical situations. Clinical assessments for fluid overload (FO) are more popular in practice, though the individual elements are imprecise and may underestimate FO. There is need to determine the performance of a locally-developed clinical score (CS) in fluid status assessment when evaluated against BIA.

Research motivation

This study was motivated by the need to derive a local method of assessing fluid status in patients on HD and determine how this method compares with the BIA.

Research objectives

The objectives of this study were to assess the hydration status of patients on maintenance HD using BIA and a CS, as well as to evaluate the performance of that CS against BIA in fluid status assessment.

Research methods

This was a single-centre, hospital-based cross-sectional study which recruited adult patients with CKD who were on maintenance HD. The patients were aged 18 years and above and had been on maintenance HD for at least 3 mo. Those with pacemakers, metallic implants, or bilateral limb amputations were excluded. Data on the participants' clinical history, physical examination, and chest radiograph findings were collected. BIA was performed on each of the study participants using the Quantum® II bio-impedance analyser manufactured by RJL Systems together with the BC 4® software. In evaluating the performance of the CS, BIA was considered as the gold standard test.

Research results

From 100 patients on maintenance HD screened for eligibility, 80 were recruited into this study. Seventy-one (88.75%) patients were fluid overloaded when evaluated using BIA with mean extracellular volume of 3.02 ± 1.79 L as opposed to the forty-seven (58.25%) patients who had FO when evaluated using the CS ($P < 0.0001$, 95% confidence interval: 0.1758-0.4242). The best cut-off point identified for the CS was four with values > 4 indicating FO and values 4 indicating no FO. At this cut-off point, the CS had 63% and 78% sensitivity and specificity respectively. None of the factors evaluated for association with FO showed statistical significance on the multivariable logistic regression model.

Research conclusions

Fluid overload is very prevalent in patients on chronic HD at the Kenyatta National Hospital Clinical score detects less FO when compared with BIA. The sensitivity and specificity for the CS were 63% and 78% respectively. None of the factors evaluated for association with FO showed statistical significance on the multivariable logistic regression model.

Research perspectives

Almost 90% of the patients had FO by BIA, and 57.5% had gross FO. BIA diagnosed significantly more patients with FO than the CS. The CS had a sensitivity if 63% and a specificity of 78% at a cut-off of 4.

FOOTNOTES

Author contributions: Muchiri K, Kayima JK, Ogola EN, McLigeyo S, and Kabinga SK designed and coordinated the study; Muchiri K performed all the study procedures; Ndung'u SW analysed and interpreted the data; Muchiri K, Kabinga SK, and Ndung'u SW wrote the manuscript; and all authors approved the final version of this article.

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MINIREVIEWS

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Editorial Board Member of *World Journal of Nephrology*, Gao-Fei He, MD, Doctor, Department of Urology, The Affiliated Huaihua Hospital of University of South China, Huaihua 41800, Hunan, China. 21718255@zju.edu.cn

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MINIREVIEWS

Management and outcomes of acute post-streptococcal glomerulonephritis in children

Leong Tung Ong

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Leong Tung Ong, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia

Corresponding author: Leong Tung Ong, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia. leotungong@gmail.com

Abstract

Acute post-streptococcal glomerulonephritis (APSGN) is the major cause of acute glomerulonephritis among children, especially in low- and middle-income countries. APSGN commonly occurs following pharyngitis due to the activation of antibodies and complements proteins against streptococcal antigens through the immune-complex-mediated mechanism. APSGN can be presented as acute nep-hritic syndrome, nephrotic syndrome, and rapidly progressive glomer-ulonephritis, or it may be subclinical. The management of APSGN is mainly supportive in nature with fluid restriction, anti-hypertensives, diuretics, and renal replacement therapy with dialysis, when necessary, as the disease is self-limiting. Congestive heart failure, pulmonary edema, and severe hypertension-induced encephalopathy might occur during the acute phase of APSGN due to hyper-volemia. APSGN generally has a favorable prognosis with only a small per-centage of patients with persistent urinary abnormalities, persistent hypertension, and chronic kidney disease after the acute episode of APSGN. Decreased complement levels, increased C-reactive protein, and hypoalbuminemia are associated with disease severity. Crescent formations on renal biopsy and renal insufficiency on presentation may be the predictors of disease severity and poor outcomes in APSGN in children.

Key Words: Post-streptococcal glomerulonephritis; Pediatrics; Acute kidney injury; Nephrotic-range proteinuria; Nephritic syndrome

Core Tip: Acute post-streptococcal glomerulonephritis (APSGN) is the major cause of acute glomerulonephritis among children, especially in the low- and middle-income countries. The clinical spectrum of APSGN can vary as acute nephritic syndrome, nephrotic syndrome, and rapidly progressive glomerulonephritis, or it may be subclinical. APSGN is generally self-limiting and has a good long-term prognosis. However, a small percentage of patients may have persistent urinary abnormalities, persistent hypertension, and chronic kidney disease after the acute episode of APSGN. This review discusses the management, prognosis, and outcomes of APSGN.

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INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) is the most common cause of acute glomerulonephritis among children which is mostly caused by group A beta-hemolytic streptococci (GABHS) [1]. APSGN primarily affects children aged between 3 and 12 years and is uncommon among children below age 3[2,3]. The most common presenting features of APSGN are hematuria, azotemia, hypertension, and peripheral edema[2]. The clinical spectrum of APSGN can vary as acute nephritic syndrome, nephrotic syndrome, and rapidly progressive glomerulonephritis (RPGN), or it may be subclinical[1]. Therefore, the severity of APSGN can vary among patients, and they can present with subclinical disease to RPGN requiring dialysis[4]. APSGN is generally self-limiting and has a good long-term prognosis[5].

The estimated global incidence of APSGN is 472000 cases per year with 77% of the cases from the low- and middle-income countries[6]. The rate of APSGN has decreased over the last few decades in high-income countries due to the use of antibiotics, improved socio-economic status, and improved hygiene[7]. However, APSGN remains one of the important causes of acute kidney injury among the pediatric populations and the leading cause of hospital admission in developing countries[5]. The reported estimated annual incidence of APSGN is 9.3 cases per 100000 persons in developing countries [8].

Most cases of APSGN occur following pharyngitis with streptococci rather than skin infection[9]. However, the nature of the preceding infectious disease is not associated with the clinical course and severity of APSGN[2]. The two main antigens contributing to the pathogenesis of APSGN are nephritis-associated plasmin receptor (NAPlr) and streptococcal pyrogenic exotoxin B (SPeB)[7]. The infection activates the antibodies and complement proteins against NAPlr and SPEB, through the immune complex-mediated mechanism causing aggregation of blood vessels in the glomeruli[2]. C3 is generally low in blood tests due to the activation of the alternate complete pathway[10]. However, 15%-30% of patients may have reduced C1 and C3 levels and 10% have normal complement levels[11]. This review discusses the management, prognosis, and outcomes of APSGN.

MANAGEMENT OF ACUTE GLOMERULONEPHRITIS

The management of APSGN is mainly supportive in nature as the disease is self-limiting[12]. Children who present with hypertension, generalized edema, or impaired renal function should be hospitalized to monitor the blood pressure and renal function[12]. APSGN should be managed with fluid restriction, anti-hypertensives, diuretics, and renal replacement therapy with dialysis when necessary[7] (Figure 1).

ANTIBIOTICS PROPHYLAXIS

Two randomized controlled trials showed no significant difference in the risk of developing APSGN between cefuroxime for 5 d and penicillin V for 10 d as antibiotics prophylaxis[13,14]. Furthermore, a Cochrane review of 27 trials showed that the efficacy of antibiotic treatment in preventing the development of APSGN after a throat infection is statistically insignificant[15]. Antibiotic therapy during the initial GABHS infection may help prevent the spread of infection and thereby prevent the development of APSGN[8]. However, antibiotic prophylaxis is generally not necessary in APSGN as the resolution of APSGN can occur without eradication of GABHS, and recurrence of APSGN is uncommon [7].

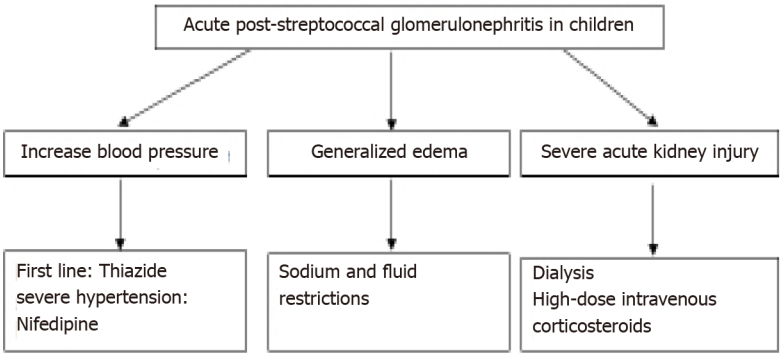

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Figure 1 Management strategy for acute post-streptococcal glomerulonephritis in children.

ANTI-HYPERTENSIVE AGENTS

Thiazide diuretics are effective as a first-line medication in APSGN; however, loop diuretics may be considered in patients with renal impairment, especially those with an estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m^2 and significant edema[8]. Thiazide diuretics are associated with electrolyte abnormalities such as hypokalemia, hyperglycemia, and hypercalcemia[16]. Therefore, serum potassium and calcium levels should be monitored when thiazides are used[16]. Hypertension in APSGN can be managed with diuretics alone or a combination of a diuretic and a vasodilator such as a calcium channel blocker to treat the hypervolemia from sodium and water retention[12]. Edematous or hypertensive patients should also be instructed on a reduced-sodium diet and may require fluid restriction[8]. Calcium channel blockers or beta-blockers may be considered in patients with the need for greater hypertension control[8]. Several studies showed that short-acting nifedipine is safe in children with severe hypertension or hypertensive emergencies and requiring a rapid reduction of blood pressure[17-19]. The minor adverse effects of short-acting nifedipine include flushing, tachycardia, edema, headache, dizziness, nausea and vomiting, pruritus, and gastrointestinal pain[18]. The occurrence of major adverse effects such as reduction in blood pressure by more than 40%, oxygen desaturation, and change in neurologic status is rare among pediatric populations[18,19]. Furthermore, several studies have shown that angiotensin-converting enzyme (ACE) inhibitors have better control of blood pressure and edema in APSGN compared to diuretics[7]. However, ACE inhibitors or angiotensin receptor blockers are usually avoided in the acute phase because they may exacerbate any reduction in glomerular ultrafiltration and hyperkalemia[12].

SODIUM AND FLUID RESTRICTION AND PULMONARY EDEMA

Patients who present with generalized edema due to acute kidney injury or acute glomerulonephritis due to APSGN may benefit from sodium restriction[20]. A sodium-restricted diet between 1 and 2 mEq/kg·d is recommended for the reduction of edema and positive natriuresis[21]. Patients who are compliant with Na^+ restriction will have self-limiting fluid restriction[21]. However, patients with severe edema may be treated with fluid restriction to two-thirds of maintenance or half or less of urine output once a brisk diuresis is achieved[21,22]. Patients who are on fluid restriction should have close monitoring of fluid input and output, serum electrolytes, and vital signs[21].

Non-cardiogenic pulmonary edema can occur due to renal failure in patients with APSGN causing acute respiratory distress syndrome[22]. The management should focus on maintaining adequate oxygenation to the lung and treat the underlying cause[23]. Non-invasive positive pressure ventilation can be used in mild cases for respiratory support while conventional mechanical ventilation and high-frequency oscillatory ventilation can be used in more severe cases while the underlying cause is being treated[24]. The pharmacological management of non-cardiogenic pulmonary edema is limited[25]. Inhaled nitrate oxide (INO) can be used in patients with pulmonary hypertension and right ventricular dysfunction to reduce the ventilation/perfusion mismatch[24]. However, corticosteroids and surfactants are not recommended as routine therapy[26].

IMMUNOSUPPRESSANTS AND DIALYSIS

Patients may require kidney biopsy if they present with undifferentiated and rapidly progressive severe acute kidney injury to exclude other causes of kidney disease which may have specific managements

[27]. High-dose intravenous corticosteroids may be used in patients who have severe clinical presentations requiring renal biopsy; however, the use of corticosteroid is based on anecdotal evidence only [28]. Immunosuppression with corticosteroids with or without an alkylating agent can be used in patients with severe crescentic glomerulonephritis (> 75% crescents) to reduce the extra-capillary inflammation[4]. However, several studies also show that immune suppressive therapy does not have a clear benefit on the long-term outcome[4]. Finally, dialysis is recommended in children with severe renal impairment causing volume excess and electrolyte abnormalities such as hyperkalemia or acidosis [12,29]. Renal replacement therapy (RRT) should be initiated in patients with overt fluid overload with cumulative fluid overload of more than 20% or more than 10% of the body weight and not responsive to diuretics[30,31]. The available modalities for RRT are intermittent hemodialysis (IH), continuous renal replacement therapy (CRRT), and peritoneal dialysis (PD) in patients with acute kidney injury due to APSGN[32]. IHD is suitable for patients who are hemodynamically stable while CRRT is more suitable for patients who are hemodynamically less stable, especially in the ICU settings[29]. PD is less suitable in critically ill patients because the dialysis depends on peritoneal circulation and there are increased risks of catheter-related infections and peritoneal fluid leakage[29].

COMPLICATIONS

The complications that might occur during the acute phase of APSGN include congestive heart failure, pulmonary edema, and severe hypertension-induced encephalopathy due to hypervolemia[10]. Serious complications such as hypertensive emergency, congestive heart failure, encephalopathy, and retinopathy were reported in 21.5%, 12.3%, 4.6%, and 1.5% of all cases of APSGN, respectively[33]. A study in French Polynesia demonstrated that 22%of the patients had severe presentations which include cardiac failure and severe hypertension with or without encephalopathy[34]. A study by Kasahara *et al* [35] showed that hypertension is the most common initial complication of APSGN with 64% of the children presenting with hypertension. Around 30%-35% of children with APSGN have been reported to have cerebral complications of hypertension[9,33]. Children with severe hypertension may present with abnormal neurological symptoms such as generalized seizures[27]. A study by Gunasekaran *et al* [33] reported that 21.5 % of children required the treatment of intravenous infusion of sodium nitroprusside in an intensive care setting due to hypertensive emergency. Anemia is the most common laboratory abnormality in patients with APSGN due to intravascular fluid overload and/or suppressed erythropoietin secretion and is significantly associated with the degree of azotemia[2].

PROGNOSIS AND OUTCOMES

Studies showed that around 34%–44% of proteinuria cases in APSGN are in the nephrotic range at APSGN onset; however, it is not associated with disease severity or renal failure[27,34]. A study done in Turkey by Demircioglu Kılıc *et al*[1] showed that hypoalbuminemia, high CRP, neutrophil count, and neutrophil/lymphocyte ratio (NLR) were associated with decreased eGFR in APSGN. Besides that, the study also showed that 75% of the 16 children with low C4 with nephrotic range proteinuria at APSGN showed decreased eGFR[1]. However, another study from New Zealand showed that none of the patients had reduced C4 among 27 patients with APSGN with severe kidney involvement[4]. On the other hand, a study by Becquet *et al* showed that patients with severe-onset APSGN had decreased C3 levels[34]. Furthermore, another study by Dagan *et al*[2] also showed that decreased C3 levels were associated with the presence of azotemia and/or full-blow nephritic syndrome. In addition to that, the study by Han *et al*[5] showed that a decrease in serum C3 level was associated with an increased rate of acute nephritic features such as edema. Decreased serum in C3 levels are found in 90% of children with APSGN and are associated with an increase in severity due to deposition of C3 glomerular subepithelial through complement activation *via* the alternate pathway[4,36]. Therefore, increased CRP, hypoalbuminemia, and hypocomplementemia are associated with disease severity and more severe clinical presentations[2].

APSGN generally has a favorable prognosis with less than 1% of children progressing to end-stage renal failure[37]. A 7-year follow-up of children with acute glomerulonephritis in Iran reported that none of the patients had hypertension or renal impairments, 3.1% had proteinuria, and 6.3% had microscopic hematuria[38]. Furthermore, a 10-year follow-up of the children that developed APSGN in Brazil demonstrated an increase in the frequency of hypertension in APSGN groups compared to control groups but no significant difference in renal function evaluation which includes serum creatinine, cystatin C, eGFR, albuminuria, and hematuria[39]. The study also showed improvement in the stabilization of median eGFR and a decrease in albuminuria in the follow-up of the same patients in 2, 5, and 10 years after the acute episode of APSGN[39]. Nevertheless, as few as 5% up to 20% of children may have persistent abnormalities in the urinary findings, either hematuria or proteinuria[2]. A 9-year follow-up study by Kasahara *et al*[35] demonstrated that serum complement levels were normalized by 12 wk after the diagnosis of APSGN, no patients had residual proteinuria by 3 years of

diagnosis, and hematuria disappeared by 4 years. However, children with APSGN in low and middle-income countries may have a poorer prognosis due to severe presentation with 30% requiring dialysis due to acute kidney injury and < 30% of the patients recovering fully[7,40].

Approximately 3% to 6% of patients with resolved APSGN may have persistent hypertension[37]. A study Vivante *et al*[41] showed that childhood glomerular disease which includes APSGB and steroid-responsive nephrotic syndrome is a risk factor of developing hypertension in adulthood. The predictors of poor long-term prognosis of APSGN include the presence of nephrotic syndrome, renal insufficiency at onset, and crescent formation on biopsy findings[8]. A retrospective study by Wong *et al*[4] reviewed 27 patients with APSGN requiring renal biopsies due to anuric renal failure, acute severe glomerulonephritis, mixed nephrotic nephritic syndrome, and delayed recovery from glomerulonephritis. The study reported that 12 patients required acute dialysis and 11 patients showed more than 50% of crescents on renal biopsies[4]. Patients with crescentic glomerulonephritis had a higher frequency of needing acute dialysis and tended to have persistent proteinuria up to 8 years of follow-up[4]. Furthermore, 8 of the 12 patients who required acute dialysis had developed ESRD, chronic renal failure, or persistent proteinuria of 2 to 4+ on urinalysis[4]. Kidney damage may persist or be superimposed years after APSGN due to persisting or secondary inflammation after infection and hyper-perfusion or hypertrophy of the nephron[42].

CONCLUSION

In conclusion, APSGN has a good prognosis and outcome in children. Severe systemic complications can occur due to severe renal inflammation and hypervolemia but are rare. Increased CRP, hypoalbuminemia, and hypocomplementemia are associated with disease severity. The predictors of severity of disease and poor outcome in APSGN in children may include the presence of nephrotic syndrome, crescent formations on renal biopsy, and renal insufficiency on presentation. A small percentage of patients may have persistent hypertension, persistent hematuria or proteinuria, or progression to chronic kidney disease following the acute episode of APSGN. Therefore, yearly follow-up is recommended to screen for any urinary abnormalities, hypertension, or renal impairment. Further prospective, multicenter, long-term studies should be conducted to evaluate the long-term outcomes of children with APSGN.

FOOTNOTES

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ORCID number: Leong Tung Ong 0000-0002-7296-7494.

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REVIEW

Acute kidney injury due to bilateral malignant ureteral obstruction: Is there an optimal mode of drainage?

Rabea Ahmed Gadelkareem, Ahmed Mahmoud Abdelraouf, Ahmed Mohammed El-Taher, Abdelfattah Ibrahim Ahmed

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Rabea Ahmed Gadelkareem, Ahmed Mahmoud Abdelraouf, Ahmed Mohammed El-Taher, Abdelfattah Ibrahim Ahmed, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Assiut 71515, Assiut, Egypt

Corresponding author: Rabea Ahmed Gadelkareem, MD, Assistant Professor, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Elgamaa Street, Assiut 71515, Assiut, Egypt. dr.rabeagad@yahoo.com

Abstract

There is a well-known relationship between malignancy and impairment of kidney functions, either in the form of acute kidney injury or chronic kidney disease. In the former, however, bilateral malignant ureteral obstruction is a surgically correctable factor of this complex pathology. It warrants urgent drainage of the kidneys in emergency settings. However, there are multiple controversies and debates about the optimal mode of drainage of the bilaterally obstructed kidneys in these patients. This review addressed most of the concerns and provided a comprehensive presentation of this topic from the recent literature. Also, we provided different perspectives on the management of the bilateral obstructed kidneys due to malignancy. Despite the frequent trials for improving the success rates and functions of ureteral stents, placement of a percutaneous nephrostomy tube remains the most recommended tool of drainage due to bilateral ureteral obstruction, especially in patients with advanced malignancy. However, the disturbance of the quality of life of those patients remains a major unresolved concern. Beside the unfavorable prognostic potential of the underlying malignancy and the various risk stratification models that have been proposed, the response of the kidney to initial drainage can be anticipated and evaluated by multiple renal prognostic factors, including increased urine output, serum creatinine trajectory, and time-to-nadir serum creatinine after drainage.

Key Words: Acute kidney injury; Kidney; Malignancy; Percutaneous nephrostomy; Ureteral obstruction; Ureter

Core Tip: Acute kidney injury due to malignant ureteral obstruction is a complex nephrological and urological emergency. Its management includes an initial resuscitation of the metabolic abnormalities, minimally invasive drainage of the obstructed kidneys, and correction of the underlying etiology. Several prognostic models have been proposed to clarify the best approach. However, there are controversies about the optimal mode of drainage of the kidneys, regarding the tool and laterality of drainage. Despite the practical preference of using the percutaneous nephrostomy rather than the double-J stent, the optimal mode of drainage has not been defined yet. The parameters of kidney response to drainage and the status of the underlying malignancy are important prognostic factors.

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INTRODUCTION

Acute kidney injury (AKI) is defined as an increase in serum creatinine (SCr) of ≥ 0.3 mg/dL (≥ 26.5 μmol/l) within 48 h or ≥ 1.5 times from the baseline within 7 d[1,2]. Classically, this biochemical definition is practically translated into a rapid deterioration of kidney functions within hours or days. It is a reversible pathology when properly managed in a timely manner. According to the positional relationship between the original pathology and the kidney of the affected patient, AKI has classically been classified into prerenal (hypovolemic), renal (intrinsic), and postrenal (obstructive; Po-AKI) AKI[2-4]. The latter class represents a urological emergency when the patient presents with disturbed kidney functions, such as an elevated SCr level. The underlying pathology of Po-AKI is the obstruction of the two kidneys or one kidney in patients with a solitary functioning kidney.

The obstruction can occur at any point along the course of the ureters. This obstruction can be caused by either benign causes such as urolithiasis or malignant causes such as bladder cancer. Kidney obstruction with elevated function warrants drainage of the kidneys as fast as possible. Methods of drainage include placement of ureteral stents or percutaneous nephrostomy (PCN) tubes. Currently, there has been no consensus on the optimal mode of drainage (method and laterality) in these cases[5,6]. Malignant ureteral obstruction (MUO) represents a more complex entity than the benign ureteral obstruction (BUO) in the field of AKI because the former has a mechanical factor (the obstruction) and a metabolic factor (the malignancy).

These variables have generated many controversies on the different aspects of the management of patients with AKI due to malignant bilaterally obstructed kidneys (BOKs). They may affect the decision-making for the mode of drainage, uncertainty of renal responses after drainage, benefits in the management of the underlying disease, and effects on patient quality of life (QoL) with the different methods of drainage[6-8]. In this commentary review, we addressed these different aspects in patients with Po-AKI due to MUO. The relevant recent literature from the last two decades was reviewed for the available approaches of drainage of BOKs in patients with MUO. The scope of the review was to clarify the efficiency of these approaches and the differences and similarities between them.

DESCRIPTION OF SUMMARIZED LITERATURE

The relevant findings from the literature are summarized as relevant findings per study (Table 1) and as a comparison of the technical and practical characteristics (Table 2). In Table 1, 36 studies were reviewed and listed in a chronological manner, including five retrospective studies published from 2000 to 2004[9-13], but one of them included patients with BUO and MUO[9]. In 2005, however, another study included patients with BUO and MUO[14], while there were another five studies that included patients with only MUO[15-19]. Only one study was found suitable in 2006, including 151 patients with MUO [20]. In 2007, three retrospective studies were reviewed with various numbers of patients[21-23]. However, five retrospective studies were found in 2008 and 2009[24-28], and three of them had comparative designs[25,27,28]. In 2010, the first prospective study was published within the time frame of this review[29]. Between 2011 and 2015, we included four retrospective studies[30-33], and only one of them had a comparative design[32]. Also, between 2016 and 2019, only four studies were reviewed [34-37], but they included two comparative studies[36,37] and one prospective study[34]. Furthermore, we included three studies published in 2020[8,38,39], one comparative study in 2021[40], and three studies in 2022[5,41,42]. Table 1 included only four prospective studies[5,29,34,40], one large data base study[8], and two multicenter studies[39,40]. Regarding the comparative data presented in Table 2, they were formulated from the studies listed in Table 1[9,12-14,17,21,33] and from other relevant studies[43,

Table 1 Summary of studies of reporting drainage of bilaterally obstructed kidneys due to malignant ureteral obstruction during the period of 2000-2022

Study		Patients			Underlying pathology		Drainage		Outcomes		
Ref.	Type	Number	Age mean ± SD or median (range) in yr	Male/female	Nature of obstruction	Primary site (IC and EC); Type of malignancy	Tool/Approach	Unilateral/bilateral	Technical success rate	Overall patient survival time and survival rate	Preference/conclusion/recommendation
Pappas *et al* [9], 2000	Retrospective, comparative	159	65.1 (18.0-94.0)	102/57	BUO (30), MUO (125), and unknown (4)	IC: bladder and prostatic (NA) EC: GIT and Gyn (NA)	PCN *vs* JJ	149/10	99% for PCN 81% for JJ	227 d	PCN is safe and effective Mean SCr improved from 6.9 mg/dL to 2.2 mg/dL
Ekici *et al* [10], 2001	Retrospective series	23	55 (25–76)	21/2	MUO	IC: bladder only (23)	PCN	NA	100%	4.9 mo	PCN is safe to avoid uremia
Chitale *et al* [11], 2002	Retrospective cohort	65	NA (53–84)	52/13	MUO	IC: bladder (30) and prostatic (28) EC: cervical (4) and rectal (3)	Retrograde (24) *vs* PCN/antegrade JJ (41)	NA	PCN: 100% JJ: 21%/98.3%	1-yr survival rate was 54.8%	Two-stage antegrade JJ was preferred
Chung *et al* [12], 2004	Retrospective cohort	101	61.4 (33.0–90.0)	44/57	BUO (11) and MUO (90)	IC: renal (2), bladder (2) and prostatic (5) EC: GIT (35), uterine (8), ovarian (5), pancreatic (2), lymphoma (12), breast (13) and other (6)	JJ	65/36	95%	NA	40.6% JJ failure at 11 mo; in 50% was due to compression
Ku *et al*[13], 2004	Retrospective, comparative	148	57.3 (20.0-84.0)	68/80	MUO	EC: NA	PCN (80)/JJ (68)	108/40	98.7%/89.0%	NA	PCN is superior to achieve decompression
Danilovic *et al*[14], 2005	Retrospective cohort	43	50.8 (25.0-84.0)	16/27	MUO (25) and BUO	IC (7): ureteral (1), bladder (1) and prostatic (4) EC (36): uterine (9), ovarian (2), colorectal (4), and other (3)	JJ initially; if failed, PCN was placed	39/4	9% (for IC)/53% (for EC)	NA	PCN might be better for patients with EC
Ganatra *et al* [15], 2005	Retrospective cohort	157	54.7 (23.0-83.0)	NA	MUO	IC: bladder (2) EC: ovarian (26),	PCN (24)/JJ (133)	NA	64.3%	11-mo survival rate was 75.8%	Bladder invasion predicts failure of JJ placement

						cervical (16), GIT (32), breast (8), testicular (6) and others (68)					
Romero *et al* [16], 2005	Retrospective cohort	43	52 (22-88)	14/29	MUO	IC: bladder (10) and prostate (5) EC: cervical (23), ovary (7), and vulva (2)	PCN	NA	100%	Mean 12-mo survival rate was 24.2%	PCN drainage is better for those <52 yr
Rosenberg *et al*[17], 2005	Retrospective, comparative	28	51 (21-78)	1/27	MUO	IC: none EC: uterine (14), ovarian (4), GIT (9) and breast (1)	Retrograde JJ; PCN alternative	NA	92%	15.3 mo; 14 patients died from malignancy during study	JJ is recommended to avoid dialysis Mean SCr improved from 2.9 mg/dL to 1.2 mg/dL
Uthappa *et al* [18], 2005	Retrospective cohort	30	61.4 (29.0-90.0)	19/11	MUO	IC: renal (2), ureteral (1), bladder (5), and prostatic (5) EC: ovarian (4), uterine (5), rectal (3), testicular (1), GIT (2), and breast (2)	Retrograde JJ; antegrade JJ was alternative	10/20	50%	NA	Retrograde JJ initial method
Wilson *et al* [19], 2005	Retrospective cohort	32	68.1 (24.0-84.0)	16/16	MUO	IC: bladder (8) and prostatic (9) EC: Gyneco-logical (7), colorectal (7), and breast (1)	PCN; JJ was a second step in 32 patients	12/20	100%	87 d	PCN is best initially and recommended when there is a definitive plan for treatment
Radecka *et al* [20], 2006	Retrospective cohort	151	73.1 (51.0-97.0)	112/39	MUO	IC: renal (4), ureteral (7), bladder (43), and prostatic (55) EC: Gyn (11), colorectal (16), and others (15)	PCN	45/106	NA	255 d; 80% died with PCN	PCN for safety and cost
Kano *et al* [21], 2007	Retrospective, comparative	75	62.7 (36.0-90.0)	30/45	MUO	IC: bladder (4) and prostate (11) EC: uterine (25), GIT (28), ovarian (4), retroperi-toneal (2), and lymphoma (1)	PCN (24)/JJ (51)	NA	100/72.5; only 78.4% of those started with JJ completed	5.9 mo and 5.6 mo for PCN and JJ, respectively	Initial trial of JJ without side holes, PCN is alternative

[1]Rosevear *et al*[22], 2007	Retrospective cohort	54	61 (32-82)	27/27	BUO and MUO	IC: prostatic (5) EC: GIT (18), lymphoma (15), ovarian (50), uterine (6), and others (4)	Retrograde JJ	21/33	81	Mean 16 mo	Retrograde JJ considered first line for MUO due to EC
Wong *et al* [23], 2007	Retrospective cohort	102	62 (31-86)	45/57	MUO	IC (30): bladder and prostatic EC: Gyn (32), GIT (21), lymphoma (5), and other (14)	PCN/Retrograde JJ	77/25	94%; 99% and 84% for PCN and JJ, respectively	6.8 mo; 12 mo rate was 29%	Prognostic factors; PCN, metastases, and MUO diagnosis in established malignancy
Ishioka *et al* [24], 2008	Retrospective cohort	140	57 (31-85)	60/80	MUO	IC: urothelial (13) EC: gastric (29), colorectal (34), ovarian (6), cervical (30) and other (23)	PCN	138/2	100%	96 d; 12-mo rate was 12% Mean SCr improved from 4.33 mg/dL to 1.39 mg/dL	Risk stratification of patients relative to 1-3 risk factors
McCullough *et al*[25], 2008	Retrospective comparative	57	69.5 (40.0-91.0)	31/26	MUO	IC: bladder (12) and prostatic (20) EC: Gyn (8), colorectal (7), lymphoma (2), and others (8)	Retrograde JJ; PCN alternative	NA	54%	SCr improved by 50% immediately after drainage	SCr level at presentation can predict success of retrograde JJ
Lienert *et al* [26], 2009	Retrospective cohort	49	71 (36-91)	27/22	MUO	IC: bladder (18) and prostatic (15) EC: colorectal (6), Gyn (5), sarcoma (2), pancreatic (2), and breast (1)	PCN	38/11	100%	174 d; 53% (prostatic) and 82% (non-prostatic) patients died during study	Risk stratification of patients; relative risk factors to validate the prognostic model of Ishioka *et al*[24]
Mishra *et al* [27], 2009	Retrospective, comparative	15	44.5 (30.0-65.0)	0/15	MUO	EC: cervical (15)	PCN; JJ alternative	1/14	100%	NA	Bilateral temporary PCN helps receive definitive or specific therapy and avoid dialysis Mean SCr improved from 7.5 mg/dL to 0.9 mg/dL within 1-3 wk
Nariculam *et al*[28], 2009	Retrospective, comparative	25	71 (51-85)	25/0	MUO	IC: prostatic only	PCN	7/18	100%	7.5-mo	Unilateral and bilateral PCN drainage were similar Mean SCr improved from 612 µmoL to 187 µmoL within 14 d
Jalbani *et al* [29], 2010	Prospective cohort	40	NA (21-70)	20/20	MUO	IC: bladder (10) and prostatic (5)	PCN	20/20	100%	350 d for IC and 25 d for EC	PCN excellent initial intervention

						EC: cervical (15), ovarian (2), rectal (3), gall bladder (1), breast (1), and lymphoma (3)					Mean SCr normalized in 62.5%
Kamiyama *et al*[30], 2011	Retrospective cohort	53	61 (32-92)	22/31	MUO	IC: prostatic (3) EC: GIT (31), Gyn (13), breast (3), and lymphoma (3)	JJ as initial tool	20/33	95.3%	Drainage success 66%	Proposed algorithm of drainage based on primary site, performance status, and degree of hydronephrosis
Migita *et al* [31], 2011	Retrospective series	25	61 (29-76)	13/12	MUO	EC: gastric (25)	Retrograde JJ (15); PCN alternative (5)	4/21	80%/100%	5.8 mo; 1-yr survival rate was 32%	Initial trial should be with JJ Prognosis is usually poor; urinary diversion should be tailored per patient
Song *et al* [32], 2012	Retrospective, comparative	75	57.1 (20.0-85.0)	0/75	MUO	EC: uterine (26), cervical (26), ovarian (20), and other (3)	Retrograde JJ; PCN alternative	66/9	81.3%; for PCN 100%	9.1 mo	Retrograde JJ first-line option; with serum cystatin C > 2.5 and obstruction length > 3 cm, PCN is alternative
Misra *et al* [33], 2013	Retrospective, case series	22	75.1 (54-87)	20/2	MUO	IC: bladder (6) and prostate (12) EC: Gyn (2) and rectal (2)	PCN; Antegrade JJ second step in 10 patients	11/11	100%/77%	78 d	PCN is effective but with significant morbidity and not prolonging life; decision of drainage made after full discussion
Cordeiro *et al* [34], 2016	Prospective cohort	208	61 (19-89)	101/107	MUO	IC: bladder (47) and prostatic (25) EC: cervical/uterine (51), ovarian (10), colorectal (45), and other (30)	Initial retrograde JJ (58); PCN as alternative (150)	107/101	27.9%/100%	144 d; 1-yr survival rate was 44.9% and 7.1% for favorable and unfavorable groups, respectively	Risk stratification model with three groups to determine usefulness of urinary diversion; favorable, intermediate, and unfavorable
Efesoy *et al* [35], 2018	Retrospective series	362	43.2	203/159	BUO and MUO (151)	IC: bladder (31) and prostatic (43) EC: cervical (57), uterine (6), ovarian (5), and rectal (9)	Ultrasound-guided PCN; Seldinger or direct puncture techniques	293/61	96.1%	NA	Ultrasound-guided PCN is recommended procedure
Tan *et al*[36], 2019	Retrospective, comparative	89	50.3 (25.0-78.0)	0/89	MUO	EC: cervical (89)	Retrograde JJ; PCN alternative	67/22	77.5%/100%	100%	No differences between JJ and PCN outcomes Drainage using JJ is preferred generally, but PCN is better in patients with severe hydronephrosis and long-segment ureteral obstruction (> 3 cm)
Tibana *et al*	Retrospective,	41	65.6 ± 9.5	23/18	MUO	IC: bladder (12)	PCN; Antegrade	10/16	NA	NA	Antegrade JJ is alternative to PCN and

[37], 2019	comparative					and prostatic (9) EC: uterine (11), ovarian (1), colorectal (7), and retroperitoneal (1)	JJ				retrograde JJ; clinical improvement in 97.5%
[2]Haas *et al* [8], 2020	Retrospective database study	238528	65.5 ± 14.6	47.6%/52.4%	MUO	IC: bladder (9.8%), prostatic (17.9%), and other (4.2%) EC: GIT (24.3%), Gyn (20.8%), lymphoma (10.3%), and other (15%)	Retrograde JJ (18%)/PCN (11.4%)	NA	NA	Death in hospital rate was 7.3%	There was a substantial variation in approaching MUO with temporal decline in use of JJ but steady use of PCN with higher use in metastatic cases Patients with urologic malignancies were older
De Lorenzis *et al*[38], 2020	Retrospective, comparative	51	70 (58-76)	20/31	MUO	EC only: colonic (28), rectal (14), gastric (5), pancreatic (3), and appendicular (1)	Retrograde JJ; PCN	30/21	80.4%/ 100%	10.5 mo; survival rate was 15.7%	GIT cancers causing MUO were associated with poor prognosis
Folkard *et al* [39], 2020	Retrospective multicenter series	105	68.8 (30.0-93.0)	55/50	MUO	IC (54): bladder and prostatic EC (51): Gyn, colorectal, and other	PCN; Antegrade JJ second step in 62%	46%/54%	100%	139 d; 4-yr survival rate was 24.8%. Only 30.5% underwent further oncological treatment	Mean SCr improved from 348 μmmol/L to 170 μmmol/L
Izumi *et al* [40], 2021	Prospective multicenter comparative	300	68 (25-96)	126/174	MUO	IC: bladder (19), ureter (13), prostatic (12), and other (6) EC: Gyn (66), GIT (121), lymphoma (26), and other (37)	PCN (44)/JJ (217)	161/139	NA	Median survival times (1-yr survival rate) of the good, intermediate, and poor risk groups were 406 (54.4%), 221 (32.7%), and 77 (8%) d, respectively	Risk stratification proposed based on primary site of malignancy, laterality of MUO, SCr level, and treatment for primary site (PLaCT); Good, intermediate and poor risk groups
Gadelkareem *et al*[5], 2022	Prospective, non-randomized	107	56.6	68/39	BUO (53) and MUO (54)	IC: bladder (30) and prostatic (5) EC: colorectal (11), cervical (6), and lymphoma (2)	PCN (79) and JJ (28)	57/50	98.3%/96.6%	NA	PCN is more suitable to MUO Mean SCr improved from 6.1 mg/dL to 1.2 mg/dL

Kbirou *et al* [41], 2022	Retrospective cohort	102	60 (36-84)	0/102	MUO	EC: cervical (95), uterine (5), and ovarian (2)	PCN (94)/JJ (8)	NA	100%	NA; 88% of patients had normalized kidney function	PCN is the main tool of drainage Early diagnosis may enable prevention of MUO
Pickersgill *et al*[42], 2022	Retrospective cohort	78	NA	NA	MUO	EC	JJ; PCN alternative	NA	Median (range) of JJ exchange was 2 (0–17)	19.9 mo	JJ failure was high, warranting early use of PCN in management of MUO

[1]Underlying malignancies were classified according to the primary site or origin as malignancy from the urological system, which was named intrinsic cancer and malignancy from other or distant systems or organs which was named extrinsic cancer.

[2]The values of the subtypes of malignancy were provided as a percentage due to the large number of cases.

BUO: Benign ureteral obstruction, EC: Extrinsic cancer, IC: Intrinsic cancer; GIT: Gastrointestinal tract, Gyn: Gynecological, JJ: Double-J stent, MUO: Malignant ureteral obstruction, PCN: Percutaneous nephrostomy, NA: Not available; SCr; Serum creatinine, SD: Standard deviation.

44]. Many prognostic and risk stratification models have been proposed so far[23,24,26,40]. They are based on variables from the patient and underlying pathology. However, the sharp stratification of these patients and solid guidelines have not been settled yet[24,26,30,34,40]. These reviewed findings will be addressed and discussed in the different sections of this review.

INCIDENCE

The incidence of AKI has been estimated by The National Institute for Health and Care Excellence as 13%-18% of people admitted to the hospital[45]. It mainly involves the elderly and has a mortality rate of 10%-80%[45,46]. Globally, AKI affects over 13 million people per year and results in 1.7 million deaths. Four in five cases of AKI occur in the developing world[47,48]. Po-AKI represents 5%-10% of all AKI cases[49]. However, it can represent up to 22% of AKI cases among the elderly[50] and 7.6% of the intensive care patients. Po-AKI due to MUO may represent up to 10% of cases with Po-AKI and 18% of patients with malignancy diagnosed within 1 year[51].

PATHOPHYSIOLOGY

Etiological classification of Po-AKI

Po-AKI is caused by urinary tract obstruction, when this obstruction affects the both functioning kidneys, a solitary kidney, or an only-functioning kidney. Relative to the origin of the obstructing pathology, the mechanism and causes of ureteral obstruction are classified into extraluminal compression, stenosis due to a mural pathology, and intraluminal lodgments. The three most common causes of renal obstruction in adults are urinary stones, malignancy, and iatrogenic benign strictures[6,7]. Hence, these causes are either malignant or benign pathologies. The benign causes include urinary

Table 2 Comparison between the drainage of kidneys with malignant ureteral obstruction by percutaneous nephrostomy *vs* double-J stent approach

[1]Variables	Drainage by PCN	Drainage by JJ
Design of catheter		
Manufacturing characteristics	One-end coil kidney tube, with a need for fixation to the skin or change by a Foley catheter after tract establishment Material: polymeric materials	Two-coil self-retaining internal ureteral catheter Material: different, including polymeric and metallic types
Route of drainage	Drain the kidney to outside the body	Drain the kidney to urinary bladder
Length	Suitable to the skin-to-pelvicalyceal distance	Suitable to the ureteral length
Mechanism of drainage	Catheter lumen only	Ureteral lumen plus catheter lumen
Procedure/Technique		
Armamentarium required	Needs radiological or ultrasonographic localization of the target calyx	Needs endoscopic armamentarium; C-arm and cystoscope
Approach	External and artificial	Internal and natural/artificial (antegrade)
Anesthesia	Mostly local	Local, epidural, or spinal
Feasibility	Independent on ureteral patency	Dependent on ureteral patency
	Equally feasible to external and internal MUO	More feasible to external (compressive) MUO
Procedural time	Longer	Shorter
Preference and indications	The advanced stages	The early stages
Success rate	High; up to 96%–100%	Relatively low, up to 85%
Drainage and complications		
Complications	They are dependent on the non-natural route (more invasive), with a greater incidence of injury of adjacent organs, hemorrhage, discomfort, obstruction, and accidental tube displacement	They are dependent on the internal route, with higher possibilities of LUTS, UTI, hematuria, and potential obstruction by underlying malignancy
Mechanism of failure of drainage	Mainly due to lumen obstruction by thick urinary contents and tube slippage	Mainly due to compression of the ureteral and stent lumens by the underlying malignancy
Effects on the outcomes		
Kidney drainage and decompression	No statistical differences, but it is better with PCN, especially with infections	Lower efficacy
Normalization of functions	No difference	
Patient survival	No difference	
Hospital stay	Longer	Shorter
Periodical change of catheter	No difference	
Overall rate of complications	No difference	
Potential effect on quality of life	Higher due to external nature of urine drainage	Lower due to internal nature of drainage

[1]The variables, classifications, and information provided in this table are drawn from the current literature, specifically within the last two decades[9,12-14,17,21,33,43,44].

MUO: Malignant ureteral obstruction; JJ: Double-J stent; LUTS: Lower urinary tract symptoms; PCN: Percutaneous nephrostomy; UTI: Urinary tract infection.

tract stones, ureteral strictures, and retroperitoneal fibrosis[7]. However, the malignant causes include both urological and extraurological malignancies[5,6]. The urological carcinomas of the urinary bladder [10,52] and prostate cancer[18] are the most common causes of MUO. The extraurological malignancies include colorectal cancer[5], cervical and uterine cancers[27], adnexal cancers, and systemic malignancy such as lymphoma and metastases (Table 1)[5,51].

Pathophysiological mechanisms of Po-AKI with MUO

Obstruction-based mechanisms: There are multiple intrinsic pathophysiological mechanisms of AKI with BOKs, including hemodynamic instability, microcirculatory disorders (such as endothelial dysfunction and microvascular thrombosis), inflammation, tubular cell injury, renal venous congestion, tubular obstruction, and auto-immune processes[53]. Reductions in renal blood flow represent a common pathologic pathway for decreasing the glomerular filtration rate in all these mechanisms[54]. However, the most likely explanation is that one adopting an occurrence of alterations in the glomerulo-tubular dysfunction due to urine flow obstruction[55]. In the early hours of obstruction of the kidney, the intraluminal pressure is transferred to the renal tubules and to Bowman's space[55]. The transferred pressure results in a decreased filtration pressure in the glomerular capillary walls. After 2-3 h of obstruction, a prostaglandin-mediated myogenic change in the afferent arterioles increases the renal blood flow, which normalizes within 5 h.

After 1 d, the renal and intraglomerular blood flow decreases as a result of the intrarenal production of thromboxane A2 and angiotensin II. These products are strong vasoconstrictors of the afferent and efferent arterioles and contribute to the reduction of the glomerular filtration rate[55]. Thromboxane A2 and angiotensin II cause contraction of the mesangial cells, decreasing the glomerular surface area that is used for filtration. After 2 d, increased thromboxane A2 reduces kidney plasma by 60%. With persistence of obstruction, more losses occur in the tubular brush epithelia and renal blood flow[56]. In addition, alterations in physiological sodium and water reabsorption are noted. Sodium absorption increases in the proximal tubules, but this increase is associated with a more significant decrease in sodium absorption in the juxtaglomerular nephrons. Furthermore, there is a reduction in the medullary ability to concentrate urine to only 350–400 mOsm[51,55,57]. This decrease in tonicity results in a drop in water absorption in the descending part of the loop of Henle. Metabolic acidosis and hyperkalemia are common in Po-AKI due to many factors, representing a failure of renal acidification. This occurs with the inability to excrete potassium and hydrogen, which is explained by distal renal tubular acidosis and Na-K-ATPase failure, resulting in hyperkalemia[51].

Malignancy-based pathophysiological mechanisms: There is a well-established relationship between malignancy and impairment of renal functions. These intimate relationships have led to the evolution of a new branch of nephrology that is concerned with associations of cancer with the renal diseases. It is not only malignancy that affects kidney function by ureteral obstruction, but also various nephropathies are associated with its hematopoietic, chemotherapeutic and immunotherapeutic effects of different types of malignancy. These nephropathies manifest clinically as proteinuria, hematuria, hypertension, and cancer related-chronic kidney disease[58-60].

AKI in patients with malignancy is relatively common. According to a study conducted on 37000 malignancy patients over a 5-year period, 27% of those patients developed AKI, and 7.6% of them developed severe AKI requiring dialysis. Also, the risk of AKI within the first year after a cancer diagnosis can be more than 18% in malignancy patients[51,61]. The non-obstructive causes of AKI in patients with malignancy include sepsis due to low immunity and bad general conditions, direct kidney injury due to the primary malignancy, metabolic disturbances, and nephrotoxic effects of chemo-therapies. In turn, AKI increases the risk of toxic effects from systemic chemotherapy, threatening their continuation[62].

The development of ureteral obstruction in the course of any malignancy is considered a sign of disease progression and reduces the median survival to < 1 year[21,24,34]. MUO is a bad event that is usually associated with advanced, and often, incurable stages of malignancy. Further, it is a definitive cause of urosepsis, acute pain, and uremic syndrome. Unilateral or bilateral MUO is due to extrinsic compression or direct infiltration by a local primary tumor or retroperitoneal lymphadenopathy. It may occur in patients with a previously diagnosed malignancy up to 84%. The median patient age at MUO diagnosis is usually high (Table 1), and the median time for development of MUO after the diagnosis of primary malignancy is variable[5,23]. In comparison, the obstruction-based mechanisms seem to have a more favorable prognosis than the malignancy-based mechanisms. The effect of the benign mechanisms is usually unifactorial and reversible by a prompt drainage of the kidneys. In contrast, the malignancy-based mechanisms are virtually multifactorial and irreversible in most instances[62]. Hence, MUO is a modifiable risk factor of morbidity and mortality in patients with Po-AKI due to malignancy. Drainage of the obstructed kidneys can prevent the major sequelae of the obstruction-based mechanisms, promptly reversing the acute deteriorations of renal functions within days or weeks[5].

CLINICAL PRESENTATION

In Po-AKI, the clinical presentation includes the general manifestations of uremia and manifestations of urinary tract obstruction. The latter may include loin pain secondary to stretching of the urinary collecting system and hematuria caused by the obstructing malignancy[63]. Decrease in urine output is a common presentation, but it is not specific to Po-AKI[41,51]. Patients with Po-AKI may present with loin tenderness and fever when obstruction is associated with infection[51,57].

DIAGNOSIS

The initial laboratory evaluation should include measurement of blood gases and electrolyte levels, SCr, blood urea nitrogen, and complete blood count. Urinalysis may be requested in cases with a preserved urine output. Then, AKI could be diagnosed and staged according to KDIGO guidelines. In Po-AKI, the hallmark of diagnosis is the presence of hydronephrosis on abdominal ultrasonography (US) or computed tomography[41]. Hydronephrosis can easily be demonstrated by the grey scale US where pelvicalyceal dilatation is recognized with or without disappearance of the renal papillae[51]. After 3 to 4 wk of obstruction, diffuse thinning of the renal cortex and the medullary tissue is mostly recognizable. Moreover, Doppler US can evaluate the blood perfusion of the kidneys themselves by measuring the resistive index and ureteral obstruction by evaluation of the ureteral jets. The absence or decreased frequency of ureteral jets may indicate urinary obstruction. The severity of ureteric obstruction can be determined by evaluating all jet dynamics, including velocity, duration, and frequency[64]. However, computed tomography is still the most diagnostic tool of Po-AKI due to benign and malignant causes [5].

MANAGEMENT

Initial measures of management

While the management of the prerenal and renal types of AKI is mainly supportive in nature, drainage of BOKs is the cornerstone of management of Po-AKI. However, the initial conservative management of patients with Po-AKI is mostly similar to that of the other types. It consists of resuscitation and correction of the metabolic imbalances[41]. However, temporary drainage of BOKs is a mandatory and principal intervention, keeping the correction of the underlying cause to a time after recovery from AKI.

A urethral catheter placement can be performed in cases of bladder outlet obstruction such as benign prostatic hyperplasia, but PCN or double-J stent (JJ) are the usual methods in the cases of ureteral obstruction[2,4,65]. Then, the broad-line goals of management are to correct the biochemical abnormalities such as severe metabolic acidosis and hyperkalemia, prevent further injury or progression to chronic kidney disease, and treat the underlying pathology[65]. The management of hyperkalemia includes prevention of the life-threatening cardiac arrhythmias by administering calcium-based salts, support of shifting potassium into the cells, and enhancement of elimination of potassium through cation exchange resins[65,66].

Despite their fundamental roles, these pharmacological and conservative interventions may have a lower effect in the management of Po-AKI than in the management of the other types, relative to the role of drainage[51,57]. Renal replacement therapy is considered in specific circumstances, such as the progression of complications in the severe cases with pulmonary edema, persistent hyperkalemia, and disturbed consciousness. This therapy is mostly in the form of intermittent hemodialysis, but peritoneal dialysis may be performed in a few circumstances[41,51,67].

Regarding the practical aspect of prioritizing dialysis over drainage, there is a perspective that underscores whether the degree of elevation of SCr alone is an indicator to resort to dialysis before drainage[41]. It can be preferable to drain one or both kidneys whenever the patient can withstand the intervention for placement of a PCN[5]. This might augment the chances of recovery with the conservative management and in those patients who may still warrant temporary dialysis after drainage. Despite the drainage efficacy, dialysis could also play an important role in the management of those patients, especially when drainage is not preferable, such as in patients with a very poor prognosis[52,68].

Drainage of BOKs

Currently, there is no consensus or well-established guidelines addressing the proper drainage of MUO, leading to wide variations in the practice patterns and preferences[5,69,70]. However, relieving MUO prevents death from progressive renal failure and possibly prolongs the patient survival[20,24]. There are two modalities for drainage of the kidneys with MUO: PCN and JJ. Both methods can cause considerable morbidity and reduce a patient's health–related QoL. There are multiple studies that compared both of them and their impact on QoL in MUO because those patients are usually in late stages and their QoL is already impaired[9,71]. The use of JJ for drainage of BOKs has many challenges, including higher invasiveness, need of anesthesia, liability of obstruction, and impossible placement due to complete obliteration of the ureteral lumen. These limitations are potentially present with antegrade and retrograde placement[72,73]. These challenges led to the development of the JJ characteristics, ranging from the new materials to the pressure-based capabilities. JJ has different types, ranging from the conventional polymeric stents to the malignancy-specifically designed stents. Among the latter, there are 3 important types that have gained popularity in recent years and are used in MUO: tandem ureteric stent; metallic stent; and metal-mesh ureteral stents. Many studies have concluded very high rates of stent failure in MUO because the tumor or lymphadenopathy compresses the ureter against the indwelling stent, persistently obliterating the tube lumen and limiting the extraluminal flow[74,75].

Also, the ureteral stent promotes mucous production from the urothelium and leads to urothelial sloughing. The lumen of a ureteral stent can become occluded with this debris[76-78].

Metallic ureteral stents gained superiority over the conventional JJ as they have a low occlusion rate, high success rate (60%) at 1 year, and low failure rate (15.4%)[79]. Considering that the median survival time with extrinsic MUO is about 1 year[24,34], there is a high possibility that metallic stent replacement is unnecessary during a patient's life. Tandem ureteric stent consists of a side-by-side ureteric stents within the ureter and can resist obstruction by providing a space in between the two stents that is difficult to compress. It has a success rate of approximately 87% at 2 years[80]. It has a range of exchange from 6 mo to 1 year[76,80]. Success rates ranged from 88% for the Allium stent to 65% for the Memokath 051. Resonance stent demonstrated the lowest migration rate (1%). Uventa showed the lowest obstruction rate (6%). A comparative study conducted by Chen *et al*[81] reported that metallic stents have longer indwelling time and are superior to conventional polymeric stents. There is a mean increase in functional duration of 4 mo, using the Resonance stent when it is compared to conventional polymeric stent[75].

Although PCN has a high success rate[13] and is considered safer than JJ[69], its need to carry an external bag could threaten the patient QoL[69]. PCN seems to be more suitable for patients with advanced malignancy who may not have the candidacy for anesthesia or the ureteral patency to pass JJ. Also, they may have expected survival rates less than 12 mo that could be improved by PCN. However, the disturbance of their QoL is still the main concern, warranting estimation of the balance between the benefits and the risks[6,70]. There are no clear advantages between the two forms of urinary diversion in MUO[6] (Tables 1 and 2). However, the type of urinary diversion depends on the experience of the urologist, the existing expertise, the availability of the armamentarium, the stage of malignancy, and the urgency of the diversion[82]. In addition, it is dependent on the potential benefits of diversion at different parameters, including the radiological exposure, decrease in SCr, the overall complication rate, febrile episodes after drainage, tube exchange rate, and overall patient survival. Both drainage forms seem to have no advantage over each other in these variables[43].

However, despite the evidence-based recommendation by the recent meta-analyses in favor of the use of JJ rather than PCN in patients with MUO[43], there is an attitude that PCN is more commonly used than JJ for drainage of BOKS with MUO (Table 1). This attitude is noticeable in the single-center studies [5,8,83]. Owing to the potential of placement of wide-caliber tubes and insertion of antegrade JJ[11,37], PCN may provide the chance of obtaining high drainage capacities[44]. Also, PCN may become the only suitable method for drainage, especially in the elderly patients with advanced stages of malignancy who are not candidates for intervention[34,43], or have non-passable MUO[15,43]. On the other hand, PCN may disturb the QoL more than JJ[6,19]. This may be attributable to many potential unfavorable events with PCN such as the repeated slippage, obstruction, and urinary leakage. Hence, there should be a sufficient rationale to perform urinary diversion by PCN in patients with terminal stages of malignancy [6,57,84]. If the evidence of the effect on QoL is absent, the potential survival benefit remains the individual factor that drives the decision, which should be PCN in patients with advanced malignancy [43,84]. This may be attributed to the fact that most of these patients have no further oncological treatment chances following the diversion[39].

Laterality of drainage of BOKs with MUO has been addressed by some authors like Hyppolite *et al* [85] who concluded superiority of bilateral over unilateral drainage. However, Nariculam *et al*[28] found no difference between unilateral and bilateral drainage. The combination of the tool and side of drainage in cases of BOKs is known as the mode of drainage. Despite the continuous research, the definition of the optimal mode of drainage of BOKs is still controversial, including the cases of MUO[5, 43,70]. We may adopt the perspective of performing unilateral drainage of BOKs, unless there are bilateral infections, pain, or non-improvement of SCr after unilateral drainage. In the latter situation, bilateral drainage can be performed consecutively[5]. Similarly, the optimal mode of drainage of BOKs due to BUO is still controversial. In a recent survey study to evaluate the preferences of urologists and radiologists who may have the principal duties of interventions in cases of acute BOKs, the conclusion was to individualize the decision for each case with emergency indications for upper tract decompression by JJ *vs* PCN[86].

PROGNOSTIC PARAMETERS AFTER DRAINAGE OF BOKS DUE TO MUO

Urine output

An increase in urine output is an early sign of renal recovery in patients with oliguric AKI. This is accompanied by a reduction in the level of high SCr, followed by a plateau period, and a subsequent fall in SCr[8,54]. Usually, the increase of urine output is physiologic and self-limiting within the first 24 h after relief of obstruction. The kidneys try to normalize the internal environment of the body by fluid and electrolyte homeostasis within the early hours before returning to the normal status of the urine output[57]. The post-obstructive diuresis means increased urine output after relief of BOKs. It is defined as increased urine output > 200 mL for two consecutive hours or urine output > 3000 mL per 24 h after relief of obstruction. When this diuresis becomes excessive or is prolonged, it becomes pathologic. It is

attributed to the sudden release of the obstruction, which initiates reflex diuresis by multiple mechanisms, evoking the full capacity of the functioning nephrons[57].

There is a perspective that post-obstructive diuresis may be a sign of the acuteness of the condition and the magnitude of the renal power preserved. Also, it is believed that it is more common after drainage of BOKs due to BUO than those due to MUO[5]. For example, an obstruction by a stone is related to its migratory potential that can be sudden and complete in comparison with an infiltrating malignancy that causes a gradual obstruction[6,7]. However, this point of difference between BUO and MUO has not been sufficiently addressed in the literature. Despite its favorable prognostic values, the potential pathologic, metabolic, and circulatory risks of post-obstructive diuresis may threaten the patient's life. Hence, it should be managed properly by oral or intravenous fluid compensation and management of the electrolyte imbalances that could ensue with excessive diuresis[57].

SCr trajectory

The rate of change of SCr over time in AKI is known as the creatinine trajectory. It can be applied in both the deterioration and recovery phases[1,5]. The time factor in this topic reflects its practical importance in catching a cure in patients with MUO. SCr trajectory has attracted the attention in the management of patients with prerenal and renal AKI[87]. However, it is still not recognizable in cases of Po-AKI. Our own work on this subject has not been published yet. The SCr trajectory is a potential parameter to understand AKI during both the renal dysfunction and recovery phases. The deterioration SCr trajectory may facilitate clinical classification and subtyping of AKI, using a different parameter rather than maximal SCr change. However, it mandates knowing a predeterioration or baseline SCr level, which is often lacking for most patients admitted in an emergency setting[1,88]. On the other hand, based on SCr trajectory, the post-intervention classification facilitates understanding patient responses to early medical interventions. This could be provided by serial measures of SCr. Hence, the identification of AKI subclasses based on SCr trajectory has been proposed as a tool to improve the precision of risk stratification of patients with AKI[1,87,88].

The time-to-nadir SCr

The time needed to reach a nadir SCr or what is known as the time-to-nadir SCr after drainage of BOKs is another parameter of the responses of the kidneys to drainage. To the best of our knowledge, this parameter has not been sufficiently addressed in the literature of Po-AKI due to MUO. However, our work in this issue has revealed that large proportions of patients may fail to reach a normal nadir SCr due to the burden of malignancy. Also, the time-to-nadir in cases of MUO seems to be longer than that in the cases of BUO[5]. Furthermore, the long time-to-nadir SCr may be associated with a low predrainage urine output and high body mass index. The rationale of measurement of the time-to-nadir SCr in patients with AKI is related to the magnitudes of benefits provided by early recovery, regarding the chance of cure or early management. This issue is still controversial in patients with MUO. The time-to-nadir SCr may be significantly shorter in patients with the potential to normalize SCr than in patients without normalized SCr levels after drainage[89].

Malignancy-related factors

The literature reports that some malignancies are statistically significant predictors of worse survival (Table 1). They include the unresectable or unsuitable malignancies for chemotherapy[83], gastropancreatic[90], hormonal-resistant prostate cancers, and those requiring hemodialysis before the procedure [16]. Despite the successful drainage of BOKs in cases of MUO, the survival rate is still poor[23]. The three significant factors that can predict a short survival time after PCN in patients with advanced stage malignancy are a low serum albumin before placement of PCN (3 g/dL or less), low grade hydronephrosis (Grade 1 or 2), and a large number of events related to malignant dissemination (3 or more). Patients who had only one variable had a 69% chance of 6-mo survival, those who had two variables had a 24% survival rate, and those with three variables had a 2% survival rate[6,26]. Wong *et al*[23] identified other predictors as metastases, prior therapy, and diagnosis of MUO with a previously established malignancy. Despite developing these prognostic models, there should be a shared decision-making approach to perform invasive procedures like PCN and JJ, with a questionable degree of the effect on renal function recovery and the risk of complications. There should be a proper explanation of prognosis, subsequent treatment possibilities, and expected results before proceeding to these invasive maneuvers[42].

Current perspectives and future expectations to improve the poor prognosis

In the last decade, the literature has shown an extensive study of the predictors of the success and overall survival rates in patients with MUO. The common finding in this category of patients is the poor overall survival with advanced MUO[68,91]. Many directions have been adopted in research to define the modifiable factors affecting the outcomes of drainage of BOKs in those patients. The main direction is studying the factors related to obstruction-based sequelae of MUO. Besides the type of malignancy, the occurrence of MUO and its degree and laterality were included as risk factors[92,93]. Electrolytes and blood biochemical compounds such as serum albumin and hemoglobin levels have been found as

independent factors[94,95]. Hence, several prognostic models have been configured and published, initiating more debates on the optimal management approach[96-99]. As an overview, the ongoing fact that seems to be verified with time is that not all patients gain benefits from drainage, and treatment should be individualized to each patient[95,100]. Another direction is the improvement of the qualities and compression-bearing capabilities of the drainage tools, represented by the advances in manufacturing of JJ for MUO. In addition, the research has gone to outweighing the certainty of the benefits of interventions versus observation in those patients, considering disturbances of QoL as a principal factor in decision-making[101,102].

CONCLUSION

AKI due to MUO is a urological emergency, warranting immediate evaluation and management. The principal line of treatment is the drainage of the kidneys *via* a placement of PCN or JJ. Despite the growing relevant literature, there is no consensus on the optimal approach. Several prognostic models have been attempted to stratify those patients relative to the potential risks and justify the interventions, but the controversies persist. Hence, the decision-making should be tailored to the patient stage and status rather than to strict guidelines. This selective approach may be attributed to the presence of many prognostic factors that should be considered during management, including the QoL and the anticipated benefit of drainage with a markedly reduced life expectancy of those patients.

FOOTNOTES

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Country/Territory of origin: Egypt

ORCID number: Rabea Ahmed Gadelkareem 0000-0003-4403-2859; Ahmed Mahmoud Abdelraouf 0000-0002-7940-1573; Ahmed Mohammed El-Taher 0000-0001-7868-5749; Abdelfattah Ibrahim Ahmed 0000-0003-4643-4448.

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