ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2022 March 25; 11(2): 39-85

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Bimonthly Volume 11 Number 2 March 25, 2022

World Journal of Nephrology

Bimonthly Volume 11 Number 2 March 25, 2022

Contents

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INDEXING/ABSTRACTING

The *WJN* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

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NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Li Zuo, Ying-Yong Zhao

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-6124/editorialboard.htm

PUBLICATION DATE
March 25, 2022

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World J Nephrol 2022 March 25; 11(2): 39-57

DOI: 10.5527/wjn.v11.i2.39

ISSN 2220-6124 (online)

REVIEW

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

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Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Patoulias D, Greece

Received: March 26, 2021
Peer-review started: March 26, 2021
First decision: October 17, 2021
Revised: October 30, 2021
Accepted: March 23, 2022
Article in press: March 23, 2022
Published online: March 25, 2022

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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.

Citation: Canaud B, Kooman JP, Selby NM, Taal M, Maierhofer A, Kopperschmidt P, Francis S, Collins A, Kotanko P. Hidden risks associated with conventional short intermittent hemodialysis: A call for action to mitigate cardiovascular risk and morbidity. *World J Nephrol* 2022; 11(2): 39-57
URL: https://www.wjgnet.com/2220-6124/full/v11/i2/39.htm
DOI: https://dx.doi.org/10.5527/wjn.v11.i2.39

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).

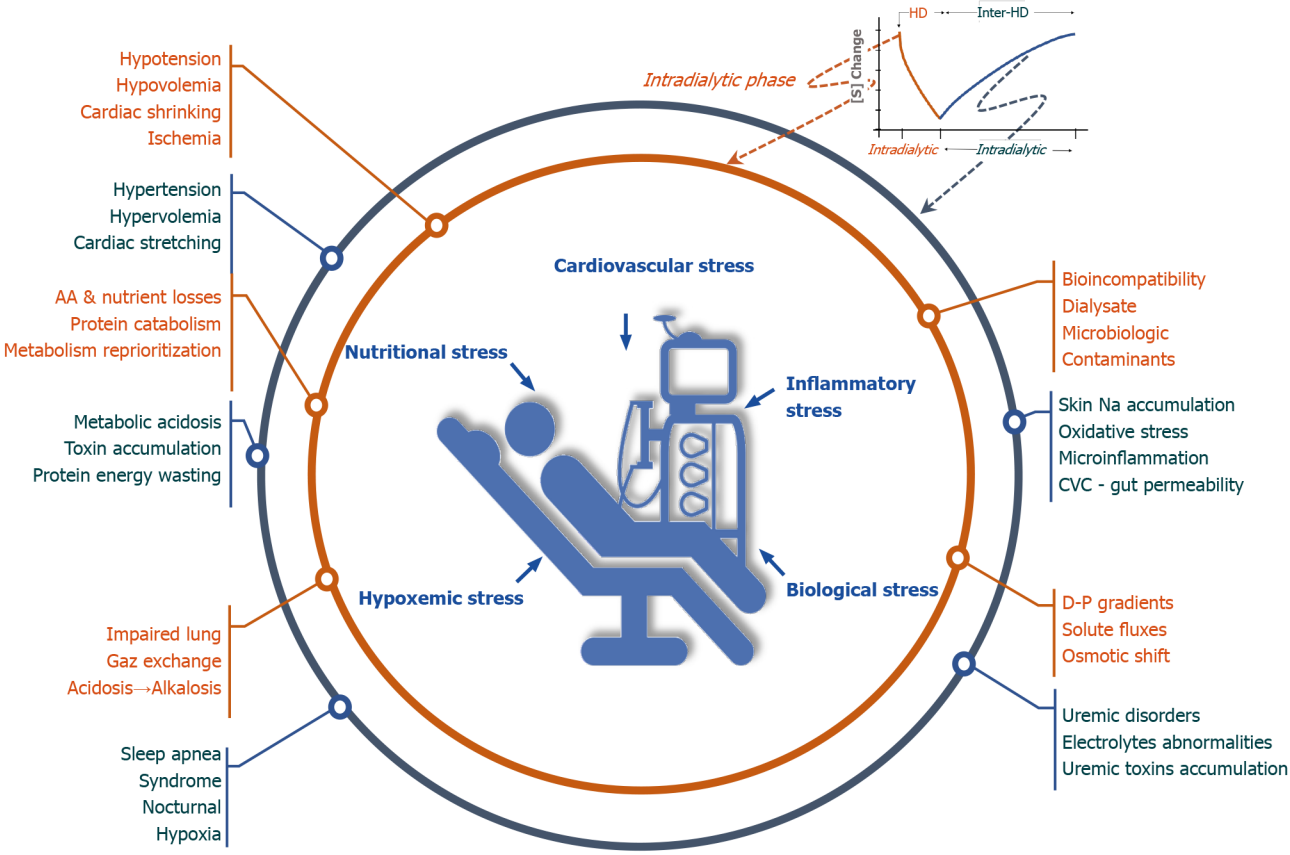
Inflammatory stress

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



DOI: 10.5527/wjn.v11.i2.39

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

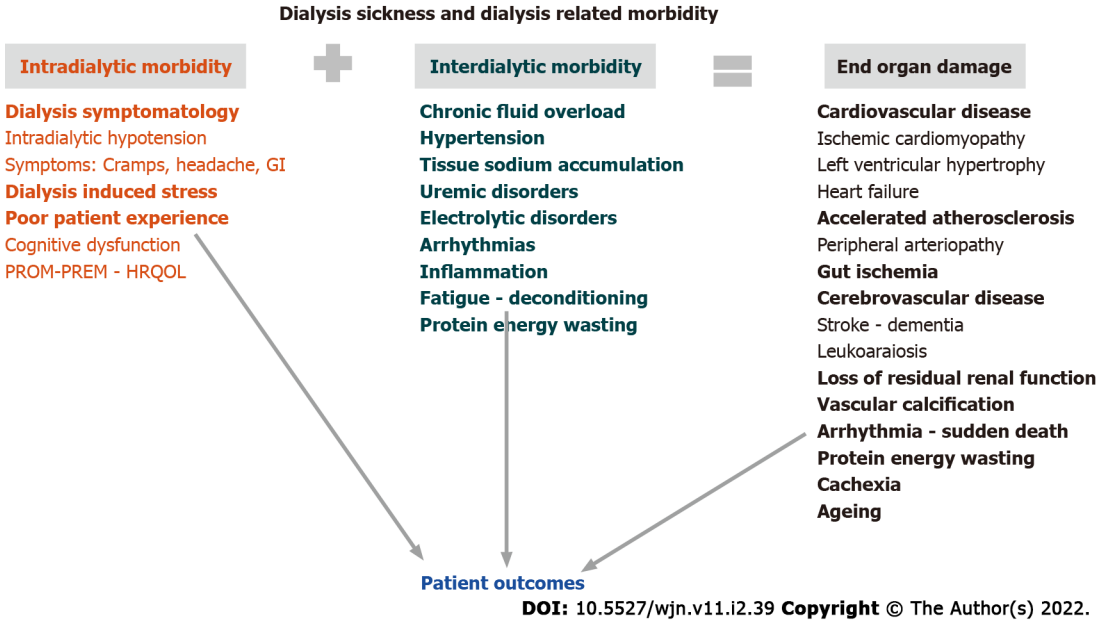


Figure 2 Dialysis Related Pathology linked to patient outcomes. GI: Glycaemic index; PROM: Patient reported outcomes measures; PREM: Patient reported experience measures; HRQOL: Health-related quality of life.

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

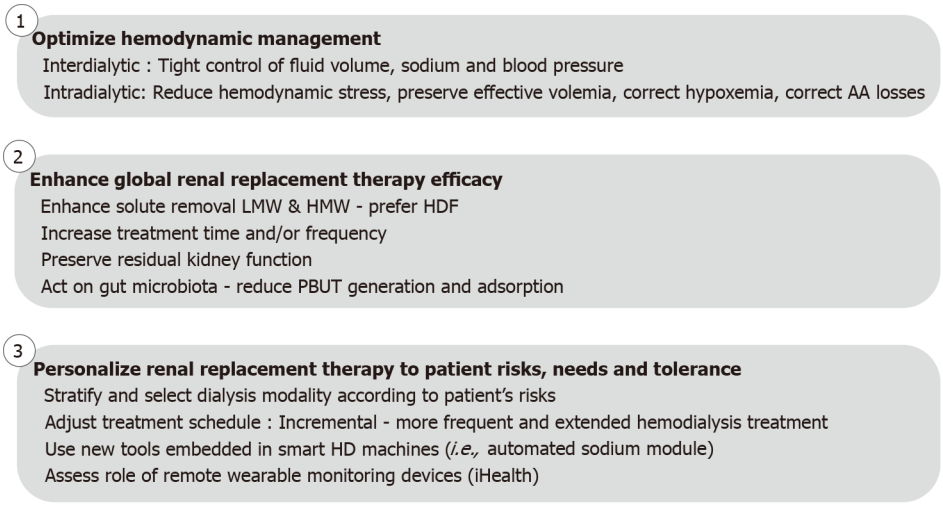
Optimizing hemodynamic management

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

Author contributions: All authors contributed equally to concept, writing, and revising of the manuscript.

Conflict-of-interest statement: Canaud B is acting as scientist consultant for FMC. No conflict of interest exists for other authors.

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S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

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World Journal of Nephrology

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World J Nephrol 2022 March 25; 11(2): 58-72

DOI: 10.5527/wjn.v11.i2.58

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

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

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Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Islam MM, Turkey; Markic D, Croatia; Shoenfeld Y, Israel

Received: October 29, 2021
Peer-review started: October 29, 2021
First decision: December 27, 2021
Revised: January 9, 2022
Accepted: March 23, 2022
Article in press: March 23, 2022
Published online: March 25, 2022

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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.

Citation: Bacharaki D, Karagiannis M, Sardeli A, Giannakopoulos P, Tziolos NR, Zoi V, Piliouras N, Arkoudis NA, Oikonomopoulos N, Tzannis K, Kavatha D, Antoniadou A, Vlahakos D, Lionaki S. Clinical presentation and outcomes of chronic dialysis patients with COVID-19: A single center experience from Greece. *World J Nephrol* 2022; 11(2): 58-72

URL: https://www.wjgnet.com/2220-6124/full/v11/i2/58.htm

DOI: https://dx.doi.org/10.5527/wjn.v11.i2.58

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

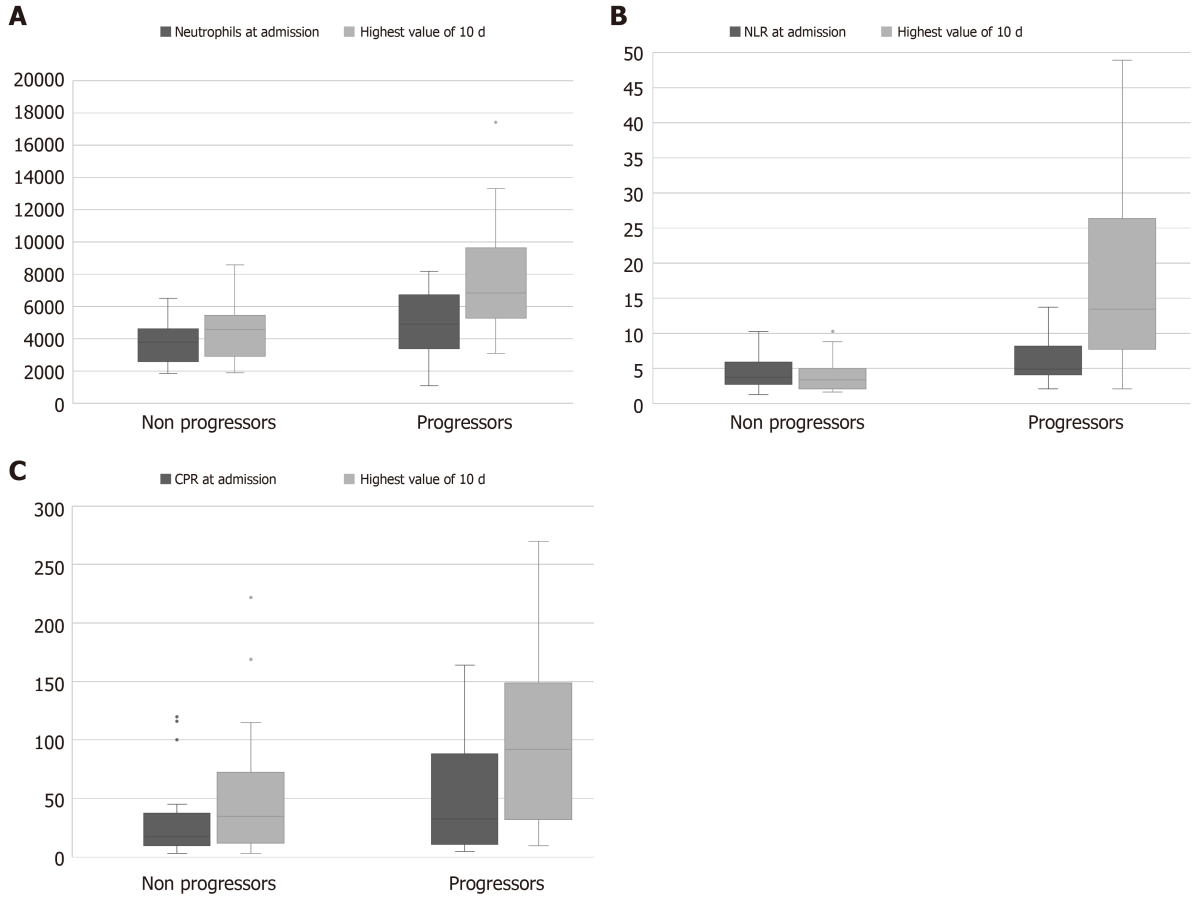
The vast majority of MHD patients in our study (90. 6%) presented with mild (50%) or moderate (40.6%) severity of COVID-19, according to the WHO classification system. Apart from symptoms, being statist-

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

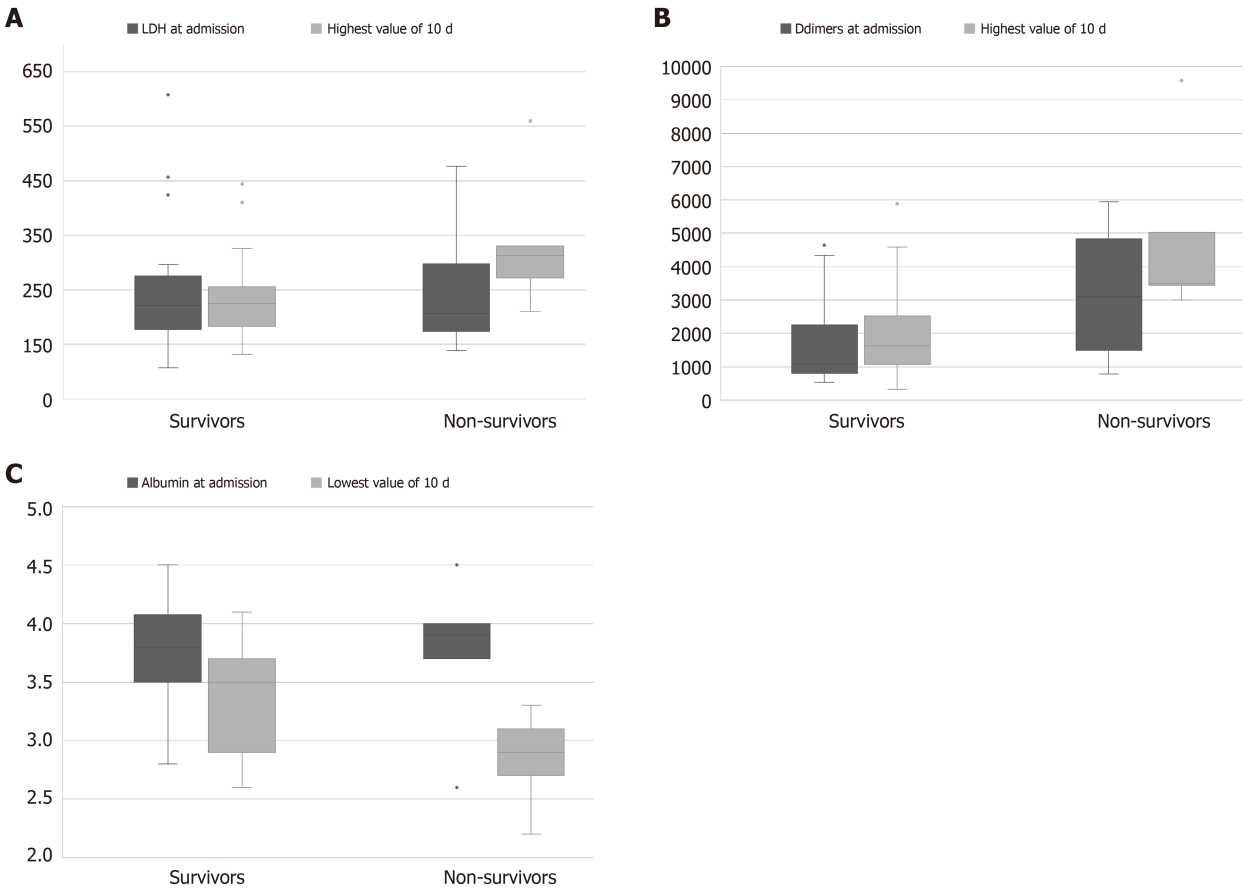
CRP: C-reactive protein; LDH: Lactate dehydrogenase; NLR: Neutrophils to lymphocytes ratio; WBC: White blood count/1000; NS: Non-significant.



DOI: 10.5527/wjn.v11.i2.58

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].



DOI: 10.5527/wjn.v11.i2.58

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.

ACKNOWLEDGEMENTS

We acknowledge the support and contribution in the management of the coronavirus disease 2019 patients from nephrologists; Kalogeropoulou S, Katsoudas S, Gounari P, Nikolopoulos P, Tsotsorou O, and nurses; Zorba I, Polymerou Z, Xoxakou L, Maniati A, Flevotomou M, Siopi D, Karasideri M, and Kyriakidis V. We acknowledge the support of Dionisios Ouzounis for the revision of tables and figures.

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.

Conflict-of-interest statement: There is no conflict of interest to disclose.

Data sharing statement: All data is available upon reasonable request from the corresponding author at bacharaki@gmail.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Xing YX
L-Editor: Wang TQ
P-Editor: Xing YX

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World Journal of Nephrology

Submit a Manuscript: https://www.f6publishing.com

World J Nephrol 2022 March 25; 11(2): 73-85

DOI: 10.5527/wjn.v11.i2.73

ISSN 2220-6124 (online)

META-ANALYSIS

Renal biopsy reports in nephritic syndrome: Update

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Specialty type: Urology and nephrology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bacharaki D, Greece; Yu F, China

Received: December 7, 2021
Peer-review started: December 7, 2021
First decision: January 25, 2022
Revised: January 31, 2022
Accepted: March 23, 2022
Article in press: March 23, 2022
Published online: March 25, 2022

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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.

Citation: Taheri S. Renal biopsy reports in nephritic syndrome: Update. *World J Nephrol* 2022; 11(2): 73-85
URL: https://www.wjgnet.com/2220-6124/full/v11/i2/73.htm
DOI: https://dx.doi.org/10.5527/wjn.v11.i2.73

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

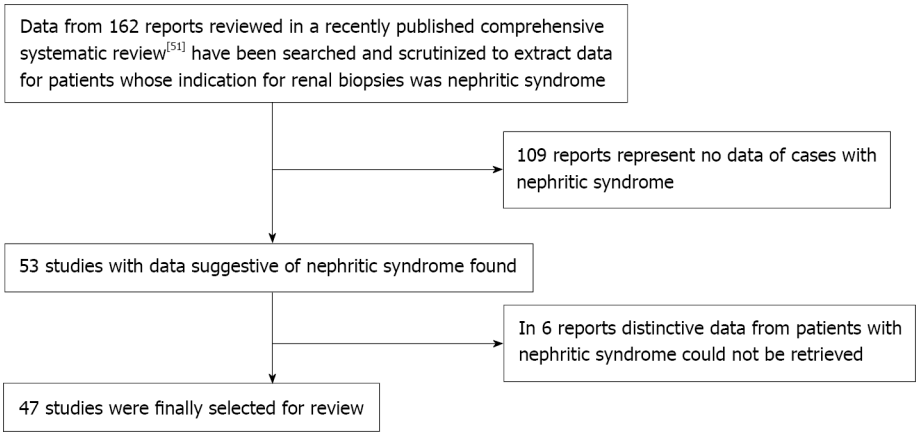
Searching and selecting reports for review

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



DOI: 10.5527/wjn.v11.i2.73

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

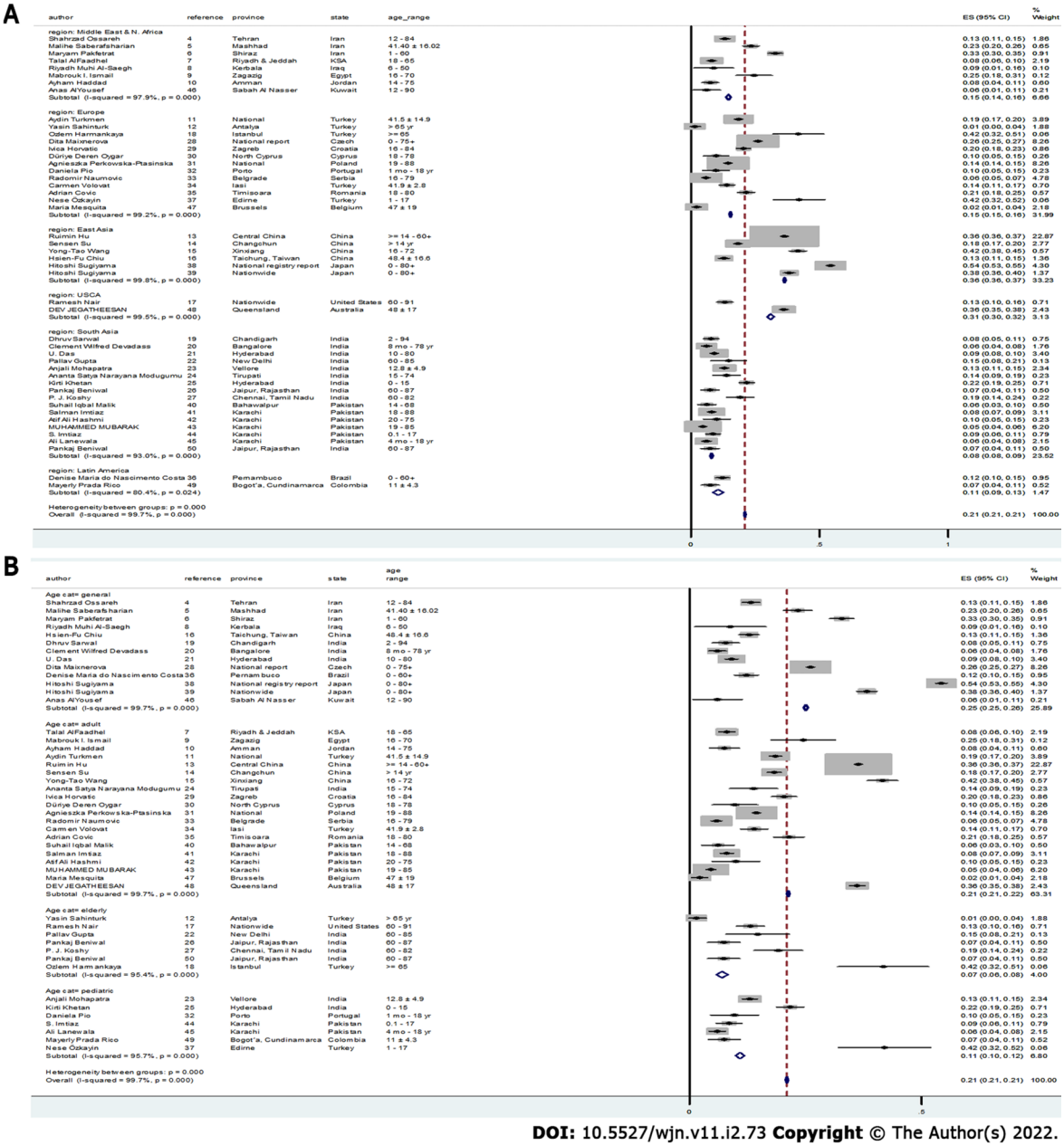
Nephropathy	Highest rate (%)	Lowest rate (%)	Pediatric (%)	Adults (%)	Elderly (%)	General (%)	NiS-NS (%)	Total (%)
MGN	M.E. 10.2 (8.1-12.3)	Eu. 2.4 (1.9-2.8)	2.5 (0.4-4.6)	7.3 (6.9-7.7)[1]	2.3 (0-5.7)	4.4 (3.9-4.8)	11.7 (6.8-16.6)	5.9 (5.6-6.2)
IgA nephropathy	E.A. 50.1 (49.3-50.8)	S.A. 9.8 (7.6-11.2)	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.



DOI: 10.5527/wjn.v11.i2.73

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

Author contributions: Taheri S performed the literature review, meta-analyses, and report preparation.

Conflict-of-interest statement: None.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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