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EDITORIAL

Advances in the pathophysiology and treatment of focal segmental glomerulosclerosis: The importance of a timely and tailored approach

Guido Gembillo, Concetto Sessa, Domenico Santoro

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Abstract

Focal segmental glomerulosclerosis (FSGS) is a histological pattern of glomerular damage that significantly contributes to chronic kidney disease and end-stage renal disease. Its incidence is rising globally, necessitating timely and personalized management strategies. This paper aims to provide an updated overview of the pathophysiology, diagnosis, and therapeutic strategies for FSGS, emphasizing the importance of early interventions and tailored treatments. This editorial synthesizes key findings from recent literature to highlight advancements in understanding and managing FSGS. Emerging evidence supports the role of targeted therapies and personalized approaches in improving outcomes for FSGS patients. Advances include novel biomarkers, genetic testing, and innovative therapeutics such as transient receptor potential ion channel blockers and antisense oligonucleotides for apolipoprotein 1-related FSGS. Effective mana-gement of FSGS requires a combination of timely diagnosis, evidence-based therapeutic strategies, and ongoing research to optimize patient outcomes and address gaps in the current understanding of the disease.

Key Words: Focal segmental glomerulosclerosis; Chronic kidney disease; Glomerulonephritis; Renal failure; Immunosuppressive therapy; Calcineurin inhibitors; Mycophenolate mofetil; Rituximab; Sparsentan; Plasmapheresis

Core Tip: Focal and segmental glomerulosclerosis is currently considered a histologic pattern encompassing several clinicopathologic entities. Its incidence is increasing worldwide. The rising prevalence is likely due to improved diagnosis and recognition of the disease, combined with a better understanding of the pathophysiology of podocyte damage and the development of therapeutics targeting the mediators underlying this clinicopathologic condition.

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is an important cause of chronic end-stage renal failure worldwide and represents a significant burden on the healthcare system. FSGS is a histological lesion characterized by the presence of sclerosis in some (segmental) portions of some (focal) glomeruli and is associated with podocyte damage. Although FSGS has been considered in the past as a single disease, it represents a heterogeneous entity in terms of etiology, clinical course and therapeutic approach. The common feature is podocyte damage and loss, which may be a primary or secondary consequence of maladaptive responses to glomerular stressors[1].

FSGS has an annual incidence of 0.2-1.8 cases per 100000 persons, with a higher prevalence in the black population and a male-to-female ratio of 1.5[2]. The incidence of FSGS has steadily increased over the years, making it the most common glomerular disease leading to end-stage renal disease (ESRD) in the United State and the most common glomerulopathy leading to ESRD[3].

The increasing prevalence is likely due to improved diagnosis and recognition of the disease, coupled with a deeper understanding of the pathophysiology of podocyte injury and the development of therapies that target the mediators of this injury.

Several aspects are associated with a more severe prognosis in FSGS patients, including genetic influences, which are an important part of the more aggressive clinical pattern.

Current clinical guidelines emphasize the need for a better understanding of the pathogenesis, particularly the immunological etiology, and the development of more targeted therapies.

This editorial addresses the current classification of FSGS, pathophysiologic mechanisms of injury, therapeutic guidelines, and novel therapies currently under investigation[4].

We synthesized insights from recent literature published over the last decade. Articles were selected from PubMed, Web of Science and Scopus databases. The search terms used were tailored to each database to retrieve studies related to of FSGS, pathophysiologic mechanisms of injury, therapeutic guidelines, and novel therapies currently under investigation. The reference lists of the selected studies were also screened and underwent the same selection process.

ETIOPATHOLOGY OF PRIMARY FSGS

The etiopathogenesis of FSGS involves a complex interplay of podocyte injury, proteinuria, circulatory factors, and genetic predispositions. Podocyte injury represents the initial step, characterized by loss of cytoskeletal integrity and detachment from the glomerular basement membrane, leading to segmental scarring. This process is exacerbated by proteinuria, which triggers tubular injury *via* inflammatory pathways and endoplasmic reticulum stress. Circulatory permeability factors, including soluble urokinase plasminogen activator receptor (suPAR) and cardiotrophin-like cytokine factor 1 (CLCF1), further contribute by interacting with podocyte receptors, inducing foot process effacement and proteinuria. Genetic influences, particularly apolipoprotein 1 (APOL1) mutations, enhance susceptibility to podocyte dysfunction through cytotoxic effects. These mutations, combined with environmental factors, highlight the multifactorial nature of FSGS and the importance of tailored therapeutic strategies.

Podocyte damage

The typical initial event for FSGS is podocyte damage that eventually leads to podocyte depletion. Podocytes are specialized cells in the glomerulus that consist of a cell body, main processes and foot processes (FPs). The FPs form a distinct, interlocking arrangement with the FPs of adjacent podocytes, creating filtration slits that are connected by the glomerular slit diaphragm. The diaphragm, together with the apical and basal membranes of the podocytes, is interconnected by a dynamically regulated actin-based cytoskeleton, which is crucial for preserving the glomerular filtration barrier against proteinuria.

Recent evidence suggests that disruption of the actin cytoskeleton and lacunar membrane in podocytes leads to loss of podocyte FPs, their enlargement, detachment from the glomerular basement membrane and subsequent migration into Bowman's space, ultimately leading to the onset of FSGS[5].

Anti-nephrin antibodies

A recent multi-institutional study of 22 Japanese pediatric patients with FSGS investigated the possible role of anti-nephrin antibodies in recurrent FSGS after renal transplantation. Among the patients studied, 14 had non-genetic primary FSGS, of which 11 developed post-transplant relapses. In these patients, plasma anti-nephrin antibody levels were elevated before transplantation or during relapses, with a median of 899 U/mL compared to the cutoff of 231 U/mL. Renal biopsies during relapses showed punctate immunoglobulin (Ig) G deposits co-localized with nephrin and alterations in nephrin tyrosine phosphorylation, with increased spontaneously hypercholesterolemic and A proteins. After remission, anti-nephrin antibody levels decreased and biopsies showed a normal pattern without IgG deposits. In patients with genetic FSGS or without relapses, antibody levels were similar to controls and no renal changes were observed[6].

These findings suggest that circulating anti-nephrin antibodies may be involved in the pathogenesis of recurrent post-transplant FSGS through a mechanism mediated by nephrin phosphorylation. Larger and more diverse studies are needed to confirm these findings.

Circulating factors

Primary FSGS is associated with an unidentified circulating factor, with no evidence of any other underlying cause. To date, several molecules have been linked: (1) SuPAR; (2) ApoA1 isoform; (3) Cardiotrophin-like cytokine factor; (4) The cMaf-inducing protein; (5) The aAngiopoietin-like-4; and (6) CD40 L[7-11].

Indirect evidence for the existence of a circulating plasma component is the clinical response to plasmapheresis and the possible recurrence after renal transplantation[12].

Idiopathic FSGS recurs after transplantation in approximately 40% of adult and pediatric patients, occasionally within hours or days after renal transplantation[13]. These clinical observations confirm that FSGS can be related to circulating components resulting from cellular or humoral immune responses.

Genetic influence

There is considerable genetic variability in the population worldwide. Expression of the G1 and G2 alleles of the *APOL1* gene is common in 35% of African Americans, 26% of Central African communities, and 50% of West African cultures. The G1 and G2 alleles increase the risk of FSGS and resulting chronic kidney disease by 3.5-fold in 16% of cases compared to European populations, with the highest incidence occurring between the ages of 30 years and 50 years[14].

Mutations in more than 50 genes expressed in the podocytes or glomerular basement membrane have been identified as causative factors for inherited variants of FSGS, which occur mainly in adolescence. These genes include *INF2*, *alpha-actinin 4*, *transient receptor potential ion channel* (*TRPC*) *6*, *Wilms tumor 1*, *nephrotic syndrome* (*NPHS*) *1*, *NPHS2*[15]. Santín *et al*[16]selected individuals with steroid-resistant nephrotic syndrome to undertake a series of studies on podocyte-associated genes. The patients had a familial inheritance pattern, with 57% developing FSGS at remarkably young ages. The *NPHS1* gene was the predominant mutant gene among these people, and patients with NPHS1 mutations exhibited a higher likelihood of progressing to ESRD compared to those with mutations in other podocyte genes.

The incidence of genetic FSGS in adults may be underestimated, and its clinical and histologic features are not yet clearly understood. Some limited studies of adult-onset genetic FSGS show heterogeneity of clinical and histologic manifestations. Careful evaluation of adult FSGS cases that do not have characteristic symptoms of primary or secondary FSGS should include genetic testing.

Recognizing the genetic forms of FSGS in adults is crucial as this type of diagnosis significantly influences therapeutic strategies, the choice of a related living donor for kidney transplantation and the chances of success of transplantation [17].

CLASSIFICATION OF FSGS

FSGS is categorized into primary, secondary and genetic forms based on etiopathogenesis or histology[18,19]. Based on the etiopathogenetic classification, we can speak of primary or secondary FSGS. Primary FSGS is probably caused by a circulating permeability factor that is toxic to the podocytes and leads to a general dysfunction of the podocytes. It typically manifests as acute nephrotic syndrome, increased proteinuria, hypoalbuminemia and peripheral edema, with podocyte pedicle processes disappearing on more than 80% of the glomeruli[20].

Based on histology, FSGS is categorized into different histologic variants based on the appearance and location of glomerular lesions detected by renal biopsy. The most important variants[21] are mentioned in Table 1[22-26].

This classification, developed in research contexts such as the CureGN project[27], uses standardized microscopy parameters and aims to improve diagnostic accuracy and allow consistent comparisons between different types of FSGS. This approach is fundamental for establishing clinicopathologic correlations that can guide treatment[28].

TREATMENT OF FSGS

FSGS, a complex and heterogeneous pathology, can result from immunological, genetic causes or secondary conditions such as obesity and viral infections. The difficulty in achieving complete remissions has encouraged the search for new, more effective therapeutic options. So, the treatment of FSGS cannot be interpreted in a single direction. The therapy

Table 1 Focal segmental glomerulosclerosis histologic variants

Focal segmental glomerulosclerosis histologic variants	Description
Collapsing	Clinically, the disease manifests as a nephrotic syndrome and a rapid, progressive loss of kidney function. Studies in animal models and investigations in patients have identified several clinical and genetic conditions associated with this form of glomerulopathy, as well as possible pathogenetic mechanisms, which are investigated here
Cellular	Shows a proliferation of cells in the affected glomeruli, with inflammatory proliferation and glomerular segments populated with inflammatory cells
Perihilar	This form mainly affects the perihilar region of the glomerulus and is frequently observed in patients with hyperfiltration and long-term adaptation to an increased renal stress
Apical pole (tip lesion)	It mainly involves the apical region of the glomeruli and is common in patients with nephrotic syndrome and a more favorable clinical prognosis
Not otherwise specified	This is the most common form and is used for cases that do not fall under the variants described above and have a less specific histologic picture

varies according to the etiopathogenesis, depending on whether it is a primitive, secondary or genetic form. The therapeutic approach for primitive FSGS is complex and requires continuous monitoring, with therapies adjusted according to the patient's response and the occurrence of side effects. The preferred initial therapy is glucocorticoids, with calcineurin inhibitors (CNIs) being an alternative option. In cases of glucocorticoid resistance or dependence, CNIs are the second-line therapy, while other options such as mycophenolate mofetil (MMF), rituximab and adrenocorticotropic hormone (ACTH) are considered in patients who cannot tolerate or are resistant to CNIs. Treatment of relapses and continuous monitoring of renal function and proteinuria are essential for the long-term management of the disease[29,30].

In patients with primary FSGS and nephrotic syndrome (proteinuria > 3.5 g/day and serum albumin < 3.5 g/dL), glucocorticoids rather than CNIs are the first-line therapy of choice. However, in patients with a high risk of glucocorticoid toxicity (*e.g.* obesity, diabetes or advanced age), CNIs (cyclosporine or tacrolimus) may be an alternative, alone or in combination with a low dose of glucocorticoids. However, CNIs are avoided in patients with impaired renal function [estimated glomerular filtration rate (eGFR) < 30 mL/minute/1.73 m²] due to their potential nephrotoxicity. All patients receiving glucocorticoid or CNI therapy should also follow general supportive measures. In certain situations, such as pregnancy or intolerance to glucocorticoids and CNI, the use of alternative agents such as MMF, rituximab or ACTH gel may be considered, although the evidence for these drugs as an initiation of therapy is limited. During therapy with glucocorticoids or CNI, monitoring is essential: (1) Serum creatinine, electrolytes and proteinuria-creatinine ratio (UPCR) every two to four weeks for the first few months; (2) In patients receiving supportive measures only, creatinine, electrolytes and UPCR every three to four months until the parameters have stabilized; and (3) In patients receiving CNI, it is necessary to monitor blood drug levels to avoid nephrotoxicity and hyperkalemia. Normally, a kidney biopsy is not repeated unless there are signs of disease progression. Relapses are common and treatment is based on the response to initial therapy.

Glucocorticoids

If the patient initially responded positively to glucocorticoids and no significant toxicity occurred, prednisone treatment is repeated. Patients who initially respond to glucocorticoids but then relapse or show no response within 16 weeks are referred to as glucocorticoid-dependent or glucocorticoid-resistant. In these cases, the use of CNI is recommended as second-line therapy in patients who are resistant or dependent on glucocorticoids. For patients who cannot receive CNI due to toxicity or impaired renal function, MMF, rituximab and in some cases cyclophosphamide are alternative options.

CNI

In patients who initially responded to CNI without significant side effects, CNI therapy is repeated. For patients who do not respond to or cannot tolerate CNI, the following alternatives are considered MMF/enteric-coated mycophenolate sodium (EC-MPS) used in combination with low-dose glucocorticoids. It is an option for patients who do not respond to CNI or who have shown a partial response with significant toxicity. Rituximab, which is equally effective in glucocorticoid-dependent patients, but there are limited data for glucocorticoid-resistant cases. Tedesco *et al*[31] examined the use of rituximab in the management of primary FSGS in adults. Thirty-one patients were followed for at least 12 months, with a median additional follow-up of 17 months in 11 patients. At the time of initial treatment with rituximab, median proteinuria was 5.2 g/24 hours, while median creatinine was stable. Response rates to renal transplant were 39%, 52%, and 42% at 3 months, 6 months, and 12 months, respectively, with improvements in proteinuria and serum albumin levels. Rituximab has allowed many patients to reduce other immunosuppressants. Steroid-dependent patients with proteinuria less than 5 g/24 hours showed a greater probability of response to rituximab. Among patients who responded to initial treatment, many maintained remission without additional immunosuppressants or with preemptive rituximab. However, some required new courses of rituximab to maintain remission. Rituximab may therefore represent a therapeutic option in primary FSGS, particularly effective in steroid-dependent patients with proteinuria less than 5 g/24 hours, although long-term management remains uncertain, with variable responses between patients. As suggested by the studies of Wang *et al*[32] the efficacy and safety of rituximab for primary FSGS in adults. Total 14 patients were

included, mainly with glucocorticoid-dependent or frequently relapsing nephrotic syndrome, treated with 2-4 administrations of rituximab (375 mg/m² every 2-4 weeks) to achieve B cell depletion. After treatment, 7 patients achieved complete remission and most were able to discontinue glucocorticoids within 6 months. An additional 5 patients achieved partial remission, of which one relapsed and one progressed to ESRD. Rituximab has been shown to reduce the risk of relapse and dependence on glucocorticoids and immunosuppressants in adult FSGS. Cyclophosphamide, which is indicated in patients who have only partially responded to prednisone and have significant interstitial fibrosis. Its use is limited to short cycles (8-12 weeks) to reduce toxicity. ACTH is used in some studies and may be effective in glucocorticoid-dependent patients, but data are limited. Sparsentan is a potentially viable alternative that can be safely administered over a prolonged period and has a sustained antiproteinuric effect. Sparsentan appears to be a viable therapeutic option for FSGS, as evidenced by the significant decrease in proteinuria observed in the DUET study[33] and its beneficial antiproteinuric effect. Nevertheless, in the DUPLEX study[34], sparsentan did not result in a significant reduction in the overall or chronic slope of eGFR in individuals with FSGS over a two-year period. Plasmapheresis (PLEX) should also be considered in refractory cases with persistent massive proteinuria despite conventional treatments. Sparsentan, a dual endothelin and angiotensin receptor antagonist, has shown promise in recent trials. The DUET study demonstrated a 42% greater reduction in proteinuria compared to irbesartan over 8 weeks, while the DUPLEX trial confirmed sustained antiproteinuric effects and a slower decline in eGFR over 108 weeks, supporting its potential as a long-term therapy for FSGS.

Over the past, the treatment of FSGS has seen significant developments thanks to the advanced understanding of the pathogenetic mechanisms of the disease and the introduction of innovative therapies. The difficulty in achieving complete remissions has encouraged the search for new, more effective therapeutic options. Among emerging therapies, blockade of TRPC5 and TRPC6 ion channels in podocytes has shown promise for limiting cell damage and proteinuria. Emerging studies emphasize the potential of TRPC blockers in reducing proteinuria and preserving kidney function, particularly in patients with APOL1-related FSGS. Clinical trials on VX-147 have demonstrated significant proteinuria reduction, highlighting its promise in targeting APOL1 mutations[35,36]. TRPC5/6 inhibitors, such as GFB-887, are currently being investigated in clinical trials for their potential to reduce proteinuria and preserve podocyte function. A phase 2 trial of GFB-887 showed a significant reduction in proteinuria levels after 12 weeks of treatment, suggesting its potential to address podocyte injury in primary FSGS. Furthermore, specific antagonists such as sparsentan and atrasentan, which inhibit endothelin and renin-angiotensin system receptors, have shown significant benefits in renal protection. For example, the DUET study demonstrated a significant reduction in proteinuria in patients treated with sparsentan compared to irbesartan, while the DUPLEX trial highlighted its potential long-term efficacy and safety in renal protection[37]. For patients with APOL1 mutations, who are particularly at risk, new targeted therapies, such as the VX-147 inhibitor and antisense oligonucleotides, represent innovative options in clinical trials[38]. In parallel, the personalized approach based on genetic sequencing is becoming essential to identify patients with monogenic forms of the disease who may benefit from targeted therapies, such as coenzyme Q10 supplementation in specific mutations. The future of FSGS management therefore seems oriented towards multi-target and personalized therapies, with the aim of achieving stable remissions and improving patients' quality of life. Despite these promising advancements, gaps remain in translating these therapies into widespread clinical practice. Challenges include variability in patient responses and limited long-term safety data for emerging therapies. For instance, while sparsentan has shown significant short-term benefits, further large-scale studies are required to confirm its long-term renal outcomes[39]. These advances offer encouraging prospects for more effective treatment of FSGS, although there remains a need for further clinical trials to confirm the efficacy and safety of these new therapies on a large scale[38]. Future research should focus on identifying biomarkers to stratify patients for personalized treatments and exploring combination therapies that address multiple pathways involved in FSGS pathogenesis.

The use of PLEX in the treatment of primary FSGS does not find ample space in the guidelines, and is generally limited to the most severe and resistant cases, in particular for patients who, despite adequate treatment with prednisone, CNI, MMF/EC-MPS, and rituximab, still present massive proteinuria and hypoalbuminemia. In recent years, the discovery of anti-antinephrine antibodies in a subgroup of patients affected by FSGS has opened new diagnostic and therapeutic perspectives, suggesting that such antibodies could play a role in determining the increased glomerular permeability that characterizes these pathologies, leading to hypothesis that using PLEX as a good strategy. The case reported by Bressendorff *et al*[40], suggests that PLEX could be an effective and complementary treatment to glucocorticoids for patients with antinephrin-positive FSGS, especially in those with severe forms or those resistant to conventional therapy. However, the real role of antinephrin antibodies as causal factors in this pathology remains to be clarified, and further studies are necessary to consolidate the efficacy profile of PLEX in cases of FSGS associated with these antibodies. Recent advances in understanding the pathophysiology of FSGS have led to the development of targeted therapies and ongoing clinical trials aimed at improving patient outcomes. Table 2 provides a comprehensive summary of these trials, highlighting the pathways involved and the preliminary findings. These studies underscore the shift towards precision medicine and a multi-target approach in managing FSGS.

The management of FSGS is shifting towards personalized approaches, guided by genetic testing and biomarker identification. Genetic testing plays a pivotal role in diagnosing monogenic forms of FSGS and tailoring treatment strategies. For example, APOL1 risk variants have been strongly associated with FSGS in individuals of African descent, and therapies targeting these variants, such as VX-147, are currently under investigation. Similarly, coenzyme Q10 supplementation has shown promise in patients with podocin mutations.

Although these therapies show promise, their long-term efficacy and safety remain to be fully established. Further large-scale, multicenter trials are needed to confirm their impact on renal survival and patient quality of life.

Table 2 Summary of ongoing clinical trials and investigational therapies in focal segmental glomerulosclerosis

Clinical trial	Targeted pathway	Findings/observations
DUET study	Endothelin and RAS receptors	Significant reduction in proteinuria observed; effectiveness on eGFR progression remains under evaluation
DUPLEX study	Sparsentan (endothelin and RAS)	Sustained antiproteinuric effect; no significant reduction in eGFR decline over two years
VX-147 trial	APOL1-targeting	Promising results in patients with APOL1 mutations; significant proteinuria reduction observed
Rituximab trials	B-cell depletion	Reduced relapses in steroid-dependent patients; limited efficacy in steroid-resistant cases
Anti-nephrin trials	Circulating anti-nephrin antibodies	Remission seen in patients with high antibody levels; further studies required to confirm pathogenic role
Adrenocorticotropic hormone gel studies	Mechanism not fully understood	Promising results in steroid-dependent patients; additional confirmation needed in larger clinical trials

APOL1: Apolipoprotein 1; EGFR: Estimated glomerular filtration rate; RAS: Renin-angiotensin system.

Circulating biomarkers such as suPAR and CLCF1 provide additional tools for individualizing treatment. Elevated suPAR levels have been associated with podocyte dysfunction and proteinuria, offering potential for targeted immunomodulatory therapies. The integration of genetic and biomarker data into clinical practice has the potential to improve outcomes by optimizing therapy for specific patient subgroups[39].

CONCLUSION

Healthcare providers should prioritize early genetic testing and biomarker assessment to guide treatment decisions. For researchers, addressing gaps in long-term efficacy data for new therapies and developing robust biomarkers for prognosis and treatment response should be key priorities. Future research should also explore combination therapies and personalized approaches to improve patient outcomes in FSGS. FSGS remains a leading cause of ESRD and represents a major challenge due to its heterogeneous and complex pathophysiology. Effective management hinges on accurate differential diagnosis and tailored therapeutic strategies. Genetic testing should be routinely integrated into clinical practice to differentiate hereditary FSGS and inform personalized treatment plans. Therapies targeting proteinuria and preserving podocyte function, such as CNIs and sparsentan, should be prioritized, particularly in patients with nephrotic syndrome. There is an urgent need for large-scale, multicenter trials focusing on the long-term safety and efficacy of emerging therapies, such as TRPC5/6 inhibitors and endothelin receptor antagonists. Additionally, the development of predictive biomarkers, including suPAR and anti-nephrin antibodies, could improve risk stratification and therapeutic decision-making. For patients with APOL1 mutations, further studies are required to validate the efficacy of targeted therapies like VX-147 and explore potential combination treatment.

FOOTNOTES

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EDITORIAL

Essential role of kidney biopsy in diagnosing glomerular diseases amidst evolving biomarkers

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Abstract

The discussion on renal biopsies and biomarkers highlights the essential aspects of nephrology. Although novel diagnostic biomarkers are emerging, renal biopsy remains critical for accurate diagnosis and treatment owing to the lack of sufficiently validated biomarkers with high sensitivity and specificity. Puspitasari *et al* highlighted the significant changes in renal biopsy indications and histological outcomes before and after the coronavirus disease 2019 (COVID-19) pandemic, reflecting the complex interactions between clinical workflows, public health issues, and patient demographics. Although biomarkers are increasingly utilized in nephrology, their importance remains balanced with traditional practices. Advancements in precision medicine are exemplified by tests like plasma anti-phospholipase A2 receptor levels. However, the COVID-19 pandemic revealed significant vulnerabilities in nephrology services, emphasizing the necessity for adaptable and robust healthcare strategies to manage chronic conditions during global crises. In conclusion, while biomarkers are poised to assume a more prominent role in nephrology, the significance of renal biopsies and thorough histopathological analysis remains paramount in understanding complex disease processes and guiding personalized patient management. The ongoing integration of traditional diagnostic approaches with innovative biomarker strategies promises to improve patient care and long-term health outcomes.

Key Words: Kidney biopsy; Glomerular diseases; COVID-19; Glomerulonephritis diagnosis; Nephritic syndrome; Nephrotic syndrome

Core Tip: Puspitasari *et al* reported significant changes in biopsy indications and histological outcomes before and after the coronavirus disease 2019 (COVID-19) pandemic, reflecting the interconnectedness of clinical practices, public health challenges, and patient demographics. Nevertheless, the COVID-19 pandemic has revealed vulnerabilities in nephrology services, necessitating flexible management strategies for chronic conditions.

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INTRODUCTION

Renal biopsy has remained an essential tool for diagnosing and characterizing glomerular diseases for decades owing to the lack of validated and available substitute diagnostic biomarkers with high sensitivity and specificity. The most promising biomarkers have not yet been implemented in routine clinical practice because of insufficient validation in large cohorts, or because limited access or high costs prevent global implementation[1]. Consequently, most of the proposed biomarkers have not been incorporated into the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for managing glomerular diseases. Consequently, renal biopsy has maintained its relevance, and its clinical utility remains highly valuable, providing definitive histological data that can guide the diagnosis, management, and prognostication of kidney diseases. Moreover, renal histology can lead to changes in treatment decisions in approximately 40% of cases[2,3].

Most epidemiological studies on glomerular diseases involve large patient series that analyze the different histological patterns observed. These studies have shown heterogeneous results across regions, potentially influenced by demographic, genetic, environmental, and temporal factors, as well as other aspects such as variability in referral and biopsy policies between different countries and within regions[4,5]. In a recent issue of this journal, Puspitasari *et al*[6] described the frequency of renal biopsies performed and the histological patterns identified over six consecutive years, covering an initial period before the coronavirus disease 2019 (COVID-19) pandemic and a second period during and after the pandemic. Their results highlighted a dramatic reduction in the number of biopsies performed after the onset of the pandemic (2020), with lupus nephritis (LN) being the most frequently observed histological finding throughout the study period, accounting for one-third of the cases, followed by minimal change disease (MCD). After the onset of the COVID-19 pandemic, an increase in the proportion of biopsies showing LN and a significant reduction in biopsied MCD cases were observed compared with the pre-pandemic period. Although LN exhibited a frequency pattern similar to that reported in middle-income countries, where LN is the most common secondary glomerular disease in biopsies, a high proportion of MCD cases stood out[7]. As the authors noted, this high number of biopsies showing MCD might be explained by the over-representation of young individuals in the sample (40% being aged < 25 years), potentially at the expense of older individuals. There may also be some degree of overestimation of MCD diagnoses, differentiating MCD from focal segmental glomerulosclerosis can be challenging in early stages[8].

The significant changes observed in the frequencies of LN and MCD between the pre-and during/post-pandemic periods have not been consistently demonstrated in other studies[9]. These variations may reflect the influence of different biopsy criteria on renal biopsy data. During the periods of lockdown, social distancing, uncertainty, high care demand, and limited hospital bed availability, histological diagnostic efforts may have prioritized nephritic clinical phenotypes over nephrotic ones, which may have been treated empirically.

The correlation between the clinical and histopathological diagnoses in nephrology is critical, especially considering the nuances associated with nephritic and nephrotic syndromes. The predominance of nephritic syndrome in the clinical indications for biopsy in the study by Puspitasari *et al*[6], despite the higher prevalence of nephrotic syndromes reflected in the final diagnoses, raises important questions regarding clinical decision-making. Interestingly, a substantial proportion (80%) of the biopsies were diagnosed with nephrotic syndrome, and histological findings revealed a significant prevalence of nephrotic syndrome, primarily MCD and focal segmental glomerulosclerosis. This discrepancy indicates a potential gap in the understanding or identification of nephrotic syndrome manifestations, even among nephrologists, which may lead to an underestimation of nephrotic conditions that require histological evaluation.

Over the past two decades, significant progress has been made in elucidating the mechanisms underlying the pathogenesis of various glomerular diseases, thereby enhancing the development of diagnostically useful biomarkers (Figure 1). The shift towards utilizing biomarkers, as outlined in the KDIGO guidelines, reflects an evolving approach for diagnosing and managing kidney diseases. This shift is becoming increasingly essential owing to the potential risks associated with invasive diagnostic strategies, such as biopsies, and the need for shorter diagnostic times. The discovery and recommendation to measure serum antibodies against the phospholipase A2 receptor (PLA2R) in cases of nephrotic syndrome suggests a move towards more targeted treatment interventions, potentially reducing the need for invasive biopsy procedures[10]. In addition to the anti-PLA2R antibodies used for diagnosing membranous nephropathy, the detection of autoantibodies against thrombospondin type 1 domain-containing 7A and neural epidermal growth factor-like 1 may prove useful[11,12]; these antibodies are present in 10% and 16% of the cases of anti-PLA2R-negative membranous nephropathy, respectively. The recent identification of anti-nephrin antibodies as potential biomarkers for

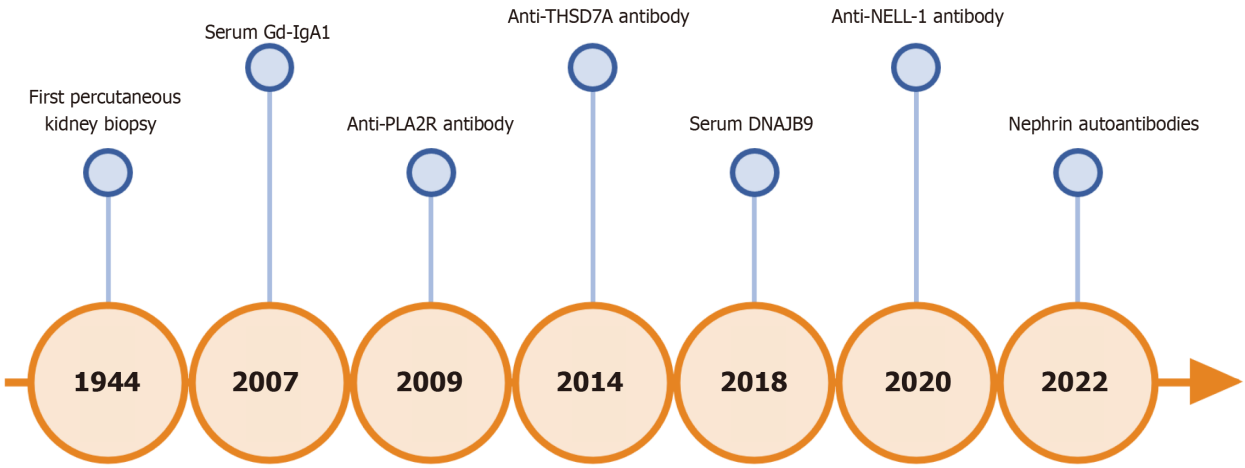

Figure 1 Timeline of the development of relevant biomarkers (useful or promising) for the diagnosis of primary glomerular diseases. Gd-IgA1: Galactose-deficient IgA1; PLA2R: M-type phospholipase A2 receptor; THSD7A: Thrombospondin type 1 domain containing 7A; DNAJB9: DnaJ homolog subfamily B member 9; NELL-1: Neural epidermal growth factor-like 1 protein.

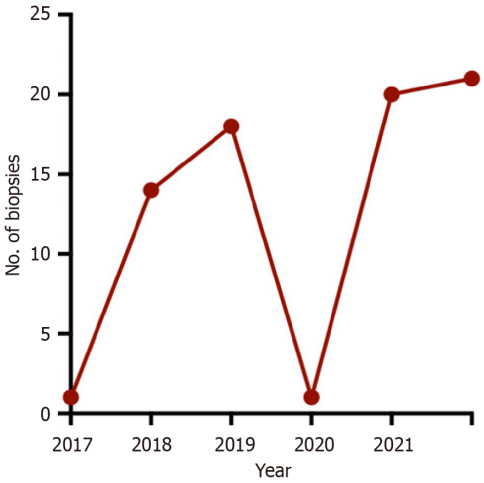

Figure 2 Trend of number of biopsies from 2017 to 2022 at Dr. Sardjito General Hospital. Citation: Puspitasari M, Wardhani Y, Sattwika PD, Wijaya W. Patterns of kidney diseases diagnosed by kidney biopsy and the impact of the COVID-19 pandemic in Yogyakarta, Indonesia: A single-center study. *World J Nephrol* 2024; 13(4): 100087. Copyright ©The Author(s) 2024. Published by Baishideng Publishing Group Inc.

podocyte diseases, particularly in diagnosing MCD, has made significant advances, although further validation and confirmation of these findings are necessary[13,14]. As the field of nephrology continues to evolve, it is likely that other serological markers (such as anti-double-stranded DNA antibodies for LN, anti-PLA2R antibodies for membranous nephropathy, and ANCAs for microscopic polyangiitis) will similarly influence clinical practice and renal biopsy decisions. Consequently, it is crucial to discover, research, and validate high-performance biomarkers to ensure that they are affordable for most centers worldwide.

Ultimately, the clinical diagnosis remains paramount in guiding the decision to perform a biopsy. Greater awareness and education regarding the different presentations of nephrotic and nephritic syndromes, along with the integration of emerging biomarkers into clinical practice, can lead to improved patient outcomes. Developing protocols that balance clinical evaluation with serological testing may streamline the diagnostic process, ensuring that patients receive timely and appropriate management of their renal condition.

The COVID-19 pandemic caused serious direct and indirect adverse health outcomes in nephrologic patients, who faced collateral reductions in access to care based on the pandemic's impact on healthcare facilities in each region. In some countries, significant reductions were observed in access to dialysis as well as in outpatient and inpatient nephrologic care. This resulted in a reduction in the number of dialysis stations, an increase in absenteeism rates, a higher patient-to-nurse ratio, and deterioration of patients' laboratory and dialysis adequacy parameters[15,16]. In addition, there was a global decline in the number of transplants and donations from living and deceased donors[17-19]. Notably, in Europe, the kidney transplantation rate decreased by 22.5%, affecting most countries[19]. This decline is particularly critical, as patients on the waiting list face greater risks of complications and mortality than those who receive transplants. Similar to the findings of Puspitasari *et al*, several reports have noted a marked reduction in the number of renal biopsies performed immediately after the onset of the pandemic, followed by an increase in the later period (Figure 2)[6,17,20,21]. The

COVID-19 pandemic and subsequent lockdowns significantly impacted various aspects of care for nephrology patients. Ensuring sustained access to optimal care for patients requiring renal replacement and complex procedures in response to future large-scale events is crucial.

CONCLUSION

In conclusion, although the identification of appropriate biomarkers is valuable, the definitive diagnosis of glomerular diseases (with a few exceptions) ultimately relies on kidney biopsies. This procedure, coupled with a thorough histopathological analysis, provides critical insights that aid clinical nephrologists in comprehending the underlying pathology affecting patients. Such an understanding is essential for guiding evidence-based treatment strategies and enhancing the prediction of medium- and long-term patient prognosis. Furthermore, accurate diagnosis and treatment planning can help select specific and non-specific therapeutic interventions—including renin-angiotensin axis blockade, inhibition of type 2 sodium-glucose co-transporter, mineralocorticoid receptor antagonism, and glucagon-like peptide-1 agonism—ensuring that therapies are tailored to the specific needs of each patient for optimal outcomes.

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REVIEW

Paediatric renal tumors: An insight into molecular characteristics, histomorphology and syndromic association

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Abstract

Paediatric renal tumors are rare and accounts for about 7% of all paediatric malignant tumors. The spectrum of paediatric renal tumors ranges from benign to malignant. Benign tumors include cystic nephroma, metanephric tumors and ossifying renal tumor of infancy. Tumor with low grade malignancy includes mesoblastic nephroma. Malignant tumors are nephroblastoma, clear cell sarcoma, malignant rhabdoid tumor, anaplastic sarcoma and Ewing sarcoma. Additionally, there are molecularly defined renal tumors, which includes renal cell carcinoma (RCC) with MiT translocations, *ALK*-rearranged RCC, eosinophilic solid and cystic RCC and SMARCB1- deficient renal medullary carcinoma. These tumors apart from having characteristic clinical presentation and histomorphology, also carry typical molecular mutations and translocations. Certain renal tumors have association with various genetic syndromes such as Beckwith-Weidmann syndrome, Wilm's tumor, aniridia, genitourinary anomalies and mental retardation syndrome, Denys-Drash syndrome, rhabdoid tumor predisposition syndrome and DICER syndrome. This review article focusses on molecular characteristics, histomorphology and syndromic association of pediatric renal tumors, their immunohistochemical approach to diagnosis with recent updates in molecularly defined renal tumors.

Key Words: Genetic syndrome; Immunohistochemistry; Paediatric; Renal tumor; Benign; Malignant; Molecular characteristics

Core Tip: This article outlines about paediatric renal tumors. They can have asymptomatic to symptomatic presentation. Every tumor has its own unique histomorphology, immunohistochemistry and molecular pathology. Certain tumors have association with genetic syndromes, which makes it prognostically more challenging for children. Knowledge and awareness of these tumors are essential for their accurate diagnosis and early treatment.

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INTRODUCTION

Renal tumors are rare in children and comprise approximately 7% of all paediatric malignant tumors. Renal tumors have variable presentation. At times they are detected incidentally and sometimes present with abdominal mass, pain or haematuria[1,2]. Renal tumors are heterogenous group of tumors, with each having their own treatment, prognosis, and relationship to genetic predispositions[2]. The spectrum of paediatric renal tumors ranges from benign to malignant[3]. Benign tumors include cystic nephroma, metanephric tumors and ossifying renal tumor of infancy (ORTI). Tumor with low grade malignancy includes mesoblastic nephroma (MN). Malignant tumors are nephroblastoma, clear cell sarcoma, malignant rhabdoid tumor, anaplastic sarcoma and Ewing sarcoma[4-6].

Molecularly defined renal tumors includes renal cell carcinoma (RCC) with MiT translocations, *ALK* driven RCC, Eosinophilic, solid and cystic (ESC) RCC (*TSC* related) and SMARCB1-deficient renal medullary carcinoma[6]. Various syndromes associated with increased risk of childhood renal tumors are DICER syndrome, rhabdoid tumor predisposition syndrome (RTPS) Denys–Drash syndrome, Wilm's tumor, aniridia, genitourinary anomalies and mental retardation (WAGR) syndrome and Beckwith-Weidmann syndrome[7-11].

The tumors can be unilateral or bilateral. Majority of the childhood renal tumors are unilateral; except paediatric cystic nephroma which can be bilateral in 25% cases and nephroblastoma which can occur bilateral in 5%-8% of cases[12-13].

BENIGN TUMORS OR TUMORS OF LOW MALIGNANT POTENTIAL

Paediatric cystic nephroma

It is a benign uncommon renal cystic neoplasm[7,14]. It is generally observed in children younger than 4 years old[14]. It accounts for 2%-3% of primary renal tumors[15]. The tumors can present as a palpable abdominal lump or can be found during screening in a child who has a germline *DICER1* mutation. The tumors are large, well-defined, comprised of cysts that vary in size and shape and lack solid nodules. The cysts contain clear fluid[7]. On histopathology, the lesion consists of cysts separated by fibrous septa; the cystic spaces are lined by flattened cuboidal epithelium, often showing hob nailing at places. Matured renal tubules are sometimes present surrounding the septae. These lesions lack blastemal component, if present, then they categorized as-cystic partially differentiated nephroblastoma[7]. The subepithelial stromal cells are Estrogen Receptor positive[16]. Molecularly paediatric cystic nephroma exhibits *DICER1* mutation[12]. Paediatric cystic nephroma are associated with DICER syndrome, which is autosomal dominant characterized by mutation in *DICER* gene [7,17].

The endoribonuclease Dicer protein of the ribonuclease III family is encoded by the *DICER1* gene, which is situated on chromosome 14. DICER 1 syndrome is a rare autosomal dominant genetic disorder that predisposes the patients to both benign and malignant tumors. It has been identified that *DICER1* germline mutations are nonsense mutations, which results in truncated proteins or nonsense-mediated RNA degradation as well as forming stop codons within the coding sequence. The spectrum of lesions observed in DICER 1 syndrome includes multinodular goiter, pleuropulmonary blastoma, cystic nephroma, Sertoli-Leydig cell tumors, Hodgkin lymphoma, pinealoblastoma, global developmental delay, lung cysts, Wilms tumors and macrocephaly[18].

On imaging study [computed tomography (CT)/magnetic resonance imaging (MRI)], the tumors appear as multilocular, cystic lesion frequently having pseudocapsule. Its differential diagnosis includes cystic Wilm's tumors[7]. These tumors are treated by complete nephrectomy and have an excellent prognosis[19]. Table 1 outlines molecular characteristics of paediatric renal tumors.

Metanephric adenoma

Metanephric adenomas are asymptomatic benign tumors, mostly diagnosed incidentally. They can be found in the age range of 5 to 84 years. It is very rare, comprising less than 0.5% of all kidney tumors. Fever, haematuria, abdominal pain and mass are presenting symptoms, if patients are symptomatic. Characteristically, at times, these patients present with polycythaemia, due to increased erythropoietin production by the neoplasm[20]. Grossly, the tumors are unifocal, well circumscribed, unencapsulated, grey white and soft to firm. Numerous calcified areas can be seen[21].

Table 1 Molecular characteristics of paediatric renal tumors

Renal tumor	Molecular feature
Paediatric cystic nephroma	*DICER1* mutation[12]
Metanephric adenoma	*BRAFV600E* mutation[25]; *KANK1::NTRK3* gene fusion in *BRAF* negative cases[26]
Metanephric stromal tumor	*BRAFV600E* mutation[32]
Metanephric adenofibroma	*BRAFV600E* mutation[35]
Ossifying renal tumor of infancy	Clonal trisomy 4[39]
MN	(1) Cellular MN: t(12;15)(p13;q25) resulting in fusion of *ETV6* and *NTRK3* genes[45]; (2) Classic MN: *EGFR* ITD[47] (3) Mixed MN: Either *EGFR* ITD or *ETV6::NTRK3* gene fusion[47]
Nephroblastoma (Wilms tumor)	Genetic changes in *WT1, CTNNB1, IGF2, TP53, MYCN* genes and 1q gain[56]
Malignant rhabdoid tumor of the kidney	Biallelic inactivation of *SMARCB1/INI1*[65]
Clear cell sarcoma of the kidney	(1) *BCOR*-ITD exon 15[74]; (2) *YWHAE: NUTM2* gene fusion[76]; (3) *BCOR::CCNB3* gene fusion[75]
Anaplastic sarcoma of the kidney	*DICER 1* and RNAase IIIb mutation[82]
Renal Ewing sarcoma	(1) t(11;22)(q24;q12) resulting *EWSR1-FLI1* fusion[89]; (2) t(21;22)(q22;q12) resulting in *EWSR1-ERG* fusion[90]
Renal cell carcinoma with MiT translocations	*TFE3* rearranged RCCs-fusion of *TFE3* with other genes like *ASPL, PRCC, PSF, CLTC*[93]; *TFEB* rearranged *RCCs-MALAT1 (Alpha)::TFEB* fusion[94]
ALK-rearranged renal cell carcinomas	*VCL-ALK* fusion[98]; *TPM3-ALK* fusion [97]; Rarely *STRN-ALK, EML4-ALK, HOOK1-ALK* fusions[96,99]
Eosinophilic solid and cystic renal cell carcinoma	Biallelic somatic mutations of *TSC1* or *TSC2* genes[106]
SMARCB1-deficient renal medullary carcinoma	Inactivation of *SMARCB1* gene[112]

MN: Mesoblastic nephroma; ITD: Internal tandem duplication.

Microscopically, MA is made up of uniformly arranged, closely spaced, small epithelial cells, having round regular nuclei and high nucleus: Cytoplasmic ratio. The tumor is mitotically inactive[22]. Psammomatous calcifications can be seen[23]. Immunohistochemically, the tumor shows dual expression for WT1 and CD57[24]. The immunohistochemical approach for definitive diagnosis is summarized in Table 2.

The most common molecular pathology observed is *BRAFV600E* mutation[25]. However, two cases have been reported having *KANK1::NTRK3* gene fusion due to t(9;15)(p24;q24) translocation; seen in *BRAF* negative cases[26].

Its differential diagnosis includes solid subtype of low-grade papillary RCC and epithelial-predominant Wilm's tumors. Metanephric adenomas are diagnosed on routine histopathological examination of the excised mass[24]. The treatment of choice is surgical resection and prognosis is better with disappearance of associated polycythaemia. However, passive seeding into perinephric lymph nodes has also been reported[27].

Metanephric stromal tumor

It is a rare benign mesenchymal renal tumor, diagnosed at 2 years of age[28]. Till date, less than 50 cases are reported in the literature. Most patients present with an abdominal mass; however, a small number of cases show signs of extrarenal vasculopathy, such as bleeding and hypertension[29]. McDonald *et al*[30] reported a case describing occurrence of metanephric stromal tumor in NF-1 patient; the patient had hypertension and the metanephric stromal tumor revealed Juxtaglomerular (JG) cell hyperplasia and florid angiodysplasia.

On histopathology, the tumor has a nodular appearance, scallop-like border, and onion skin cuffing around entrapped tubules. Vascular changes include angiodysplasia and JG cell hyperplasia. In 20% cases, heterologous elements such as glial and chondroid tissue are observed[31]. The tumor is CD34 positive[31,29]. Molecularly, the tumor has *BRAFV600E* mutation[32].

Its close differential is metanephric adenofibroma. These tumors are diagnosed on routine histopathology. Surgery is the main treatment and patients have a favorable outcome[29].

Metanephric adenofibroma

Metanephric adenofibroma is a rare biphasic renal tumor composed of epithelial and stromal components. It was previously termed as "nephrogenic adenofibroma"[33]. Patients present with haematuria and polycythaemia. Their age of presentation ranges from 13 months to 36 years. Less than 30 cases have been documented[34]. Microscopically, the tumor has dual epithelial and stromal components. The epithelial component has uniform small cuboidal cells with hyperchromatic nuclei and scant cytoplasm, forming tubules at places. The stromal component display spindle shaped cells having tapered hyperchromatic nuclei; strongly positive for CD34[33]. The molecular pathology of metanephric

Table 2 Immunohistochemistry of paediatric renal tumors

Renal tumor	Immunohistochemistry expression
Paediatric cystic nephroma	ER positive[16]
Metanephric adenoma	WT1 and CD57 positive[24]
Metanephric stromal tumor	CD34 positive[29,31]
Metanephric adenofibroma	CD34 positive[33]
Ossifying renal tumor of infancy	EMA and Vimentin positive [38]
Nephroblastoma (Wilms tumor)	The blastemal component is WT1 and PAX8 positive; the epithelial component is cytokeratin and Epithelial Membrane Antigen and positive; stromal component is vimentin positive[2]
Malignant rhabdoid tumor of the kidney	*SMARCB1/INI1* loss[64]
Clear cell sarcoma of the kidney	Cyclin D1 and BCOR positive[73]
Renal Ewing sarcoma	CD99 and NKX2-2 positive[87-88]
Renal cell carcinoma with MiT translocations	*TFE3* positive[92]
ALK-rearranged renal cell carcinomas	*ALK* positive, *INI1/SMARCB1* retained[97]
Eosinophilic solid and cystic renal cell carcinoma	*CK20* and *PAX8* positive whereas CK7 and C-kit negative[105]
SMARCB1-deficient renal medullary carcinoma	PAX8, Epithelial Membrane Antigen and vimentin positive [110]; *SMARCB1/INI1* loss[111]

adenofibroma involves *BRAFV600E* mutation[35].

Its differential includes metanephric adenoma and metanephric stromal tumor. Metanephric adenofibroma is diagnosed on histopathological examination. The treatment of choice is excision and patients have benign course with good prognosis. Interestingly, one case of metanephric adenofibroma in combination with Wilms tumors and RCC has been reported[36].

ORTI

ORTI is an intracalyceal neoplasm with male preponderance. ORTI is very rare, with approximately 25 cases reported in literature. It is diagnosed in children 6 days to 2.5 years of age. Patients present with haematuria[37]. On microscopic examination, the tumor is composed of osteoblast-like cells (ossifying component); small undifferentiated blastemal like cells and sometimes spindle cells. Mitotic activity can also be observed in few cases. The osteoblast-like cells show strong immuno-expression for Epithelial Membrane Antigen (EMA) and Vimentin[38]. Clonal trisomy 4 is seen in ORTI[39]. Diagnosis is made on histopathology. On imaging, it is seen as a calcified pelvic mass[40]. Very rarely, its differential can be Wilm's tumors with predominant heterologous osteoid differentiation. Conservative surgical care is adequate. Prognosis is favourable. Evidence of recurrence or metastasis has not been reported yet[41].

MN

Earlier it was known as congenital MN. MN accounts for 3%-4% of childhood renal tumors[42]. Most of the cases have been reported in first 9 months of life[43]. MN virtually never arises after the age of 3 years. Clinically, children present with abdominal mass[44]. It includes three subtypes: Cellular, classic and mixed[45]. Majority of the cases are diagnosed within first 9 months of life[43]. On histopathology, each subtype of MN has specific microscopic morphology.

Cellular MN: This is the most common subtype, comprising 65% cases. On gross examination, the tumor and renal parenchyma can be distinguished easily. Microscopically, the tumor is highly cellular, comprised of plump cells arranged in sheets, have vesicular nuclear chromatin, moderate cytoplasm and increased mitotic activity[46].

Classic MN: It comprises 25% of MN. In classic MN, a clear demarcation between tumor and renal parenchyma cannot be appreciated as the tumor cells are seen protruding into the renal parenchyma as finger like fashion. Islands of hyaline cartilage can be seen at tumor-parenchymal junction. The tumor displays spindle cells with collagen deposition, dilated thin-walled blood vessels and low mitotic activity[46].

Mixed MN: It comprises 10% of MN and includes features of both subtypes in varying amounts[46]. Similar to histopathology, each subtype of MN exhibits specific molecular abnormality.

Cellular MN: Chromosomal translocation t(12;15)(p13;q25) resulting in fusion of *ETV6* and *NTRK3* fusion genes[45].

Classic MN: *EGFR* internal tandem duplication (ITD)[47].

Mixed MN: Either *EGFR* ITD or *ETV6::NTRK3* gene fusion[47].

MN can be diagnosed prenatally on ultrasound and has been shown to be associated with polyhydramnios[44]. Its differential diagnosis includes Wilms tumor and neuroblastoma[48].

Treatment for MN is nephrectomy with surgical margin clearance. Chemotherapy is routinely not administered. Overall, children have an excellent prognosis. Very rarely, patients can have local relapse and metastasis to lung, liver and brain[44,49].

MALIGNANT TUMORS

Nephroblastoma (Wilms tumor)

It is a malignant embryonal tumor, usually diagnosed at the age of 3-4 years with slight female preponderance[50]. It is the most common pediatric renal cancer affecting 1 in 10000 children[50,13]. Its precursor lesion is nephrogenic rests, which is present in more than 90% of bilateral tumors and approximately 40% of unilateral tumors[51,52]. Classically, it is a triphasic tumor which includes three components - blastemal, stromal and epithelial[53]. Teratoid Wilm's tumor is termed when there is predominance of heterologous elements in the tumor tissue, such as glial, adipose, muscle, cartilage or bone. Children generally present with an abdominal mass[54].

The most important histological parameter in Wilm's tumor is anaplasia, its presence indicates high-risk tumor with worse prognosis. Anaplasia includes three characteristic features- hyperchromatic nuclei, marked nuclear enlargement with nuclear diameter at least three times those of neighboring cells and presence of enlarged atypical tripolar or multipolar mitotic figures. Anaplasia is further subdivided into focal or diffuse[55].

On immunohistochemistry, the blastemal component is positive for WT1 and PAX8; the epithelial component shows strong immunoexpression with cytokeratin and EMA whereas stromal component immunostains with vimentin[2].

Molecularly, Wilms tumor has several genetic changes, such as in *WT1* on chromosome 11p13, *CTNNB1* on chromosome 3p22, *IGF2* on chromosome 11p15, *TP53* on chromosome 17p13, *MYCN* on chromosome 2p24and 1q gain [56]. According to our literature search, we found that Wilms tumor has been associated with multiple syndromes such as WAGR syndrome, Denys–Drash syndrome, Beckwith–Wiedemann syndrome and Simpson-Golabi-Behmel Syndrome Type I[9-11,57].

The genetic syndromes associated with various paediatric renal tumors are described in Table 3 highlighting their specific renal and extra-renal manifestations.

Various studies have been conducted for understanding the management of Wilms Tumor. Amongst these, the two most revolutionizing studies were NWTS and SIOP. The National Wilms Tumor Study (NWTS), a cancer research co-operative group was formed in 1969 which emphasized on upfront surgery principle. NWTS conducted five trials, of which NWTS 1 to NWTS 4 were randomized trial whereas NWTS 5 was purely clinical trial. Each NWTS trial had a specific purpose to study, such as NWTS 1 was to ascertain how surgical technique affects the course of treatment; NWTS 2 studied the prognosis; NWTS 3 focused on reducing the course of treatment for low-risk individuals while developing more effective chemotherapy for patients who are at high-risk for relapse; NWTS 4 studied the efficacy, toxicity and cost of administration of various regimens and NWTS 5 was for identifying prognostic factors. Another group was Societe Internationale D'oncologie Pediatrique (SIOP) which started study on Wilms Tumor in 1971. SIOP gave the concept of providing preoperative chemotherapy in all stages to the patients. Preoperative chemotherapy will shrink the tumor size and would reduce the chances of intra-operative rupture of tumor. However, some researchers believe that pre-nephrectomy chemotherapy might alter the tumor's histology and would downstage the tumor[58].

For Wilms tumors, at present, Children's Oncology Group (COG) and SIOP protocols are being followed which uses a wide range of prognostic factors for guiding treatment. Stage, tumor histology, patient age, tumor weight, completeness of lung nodule response, and loss of heterozygosity at chromosomes 1p and 16q are prognostic criteria employed in the current COG research. Whereas, the current SIOP studies use tumor stage, histology, tumor volume, and therapeutic responsiveness as prognostic parameters[59].

Diagnosis of Wilms tumors can be made by combination of imaging techniques (such as ultrasound/CT scan/MRI abdomen)[60]. Triphasic Wilms tumors can easily be diagnosed on histopathology. However, monophasic component makes challenging; in such cases application of immunohistochemistry markers along with molecular study helps to arrive at a conclusive diagnosis. It should also be noted that before concluding a tumor as monophasic nephroblastoma, extensive grossing of excised mass from all representative areas should be undertaken to avoid any error. Differentials for pure blastemal Wilms tumor includes neuroblastoma, Ewing sarcoma; for pure epithelial component is metanephric adenoma, hyperplastic perilobar nephrogenic rests; and for pure stromal type includes MN and metanephric stromal tumors[2]. Treatment for nephroblastoma includes multimodal approach of chemotherapy, surgical excision and radiotherapy (if necessary)[59]. Overall survival is 90%; relapse can be seen in 15% children[61].

Malignant rhabdoid tumor of the kidney

This is the most aggressive renal parenchymal tumor, diagnosed at around 1 year of age[62]. Malignant rhabdoid tumor of the kidney (MRTK) are extremely rare tumors accounting for 2% of all paediatric renal tumors. Generally, children present with an abdominal mass. Histopathologically, various patterns are observed in MRTK, which includes classical, sclerosing, epithelioid, spindled or mixed. The individual tumor cells have large eccentrically placed vesicular nuclei with prominent nucleoli and abundant eosinophilic cytoplasm. Mitotic activity is high[63]. On immunohistochemistry, the tumor cells display loss of nuclear staining with SMARCB1/INI1[64].

Table 3 Genetic syndromes associated with paediatric renal tumors

Genetic syndromes	Renal tumors	Extra renal manifestations	Ref.
DICER 1 syndrome	Wilms tumor, cystic nephroma, anaplastic sarcoma of kidney	Pinealoblastoma, pleuropulmonary blastoma	Caroleo *et al* [83]
WAGR syndrome	Wilms tumor	Aniridia, genitourinary anomaly, developmental delay	Hol *et al*[10]
Denys–Drash syndrome	Wilms tumor, rapid progressive nephropathy	Male pseudo-hermaphroditism	Kucinskas *et al* [9]
Beckwith–Wiedemann syndrome	Wilms tumor	Hepatoblastoma, neuroblastoma, hemihypertrophy, macroglossia, macrosomia, organomegaly, omphalocele	MacFarland *et al*[11]
Simpson-Golabi-Behmel Syndrome Type I	Wilms tumor	Hepatoblastoma, adrenal neuroblastoma, macrocephaly, cardiovascular and skeletal abnormalities, visceromegaly	Tenorio *et al*[57]
Rhabdoid tumor predisposition syndrome	Malignant rhabdoid tumor of the kidney	Malignant rhabdoid tumors at various sites like central nervous system, liver, bladder, mediastinum	Nemes *et al*[66]

Molecularly, MRTK are characterized by biallelic inactivation of *SMARCB1/INI1* gene located on chromosome 22q11.23 occurring due to mutation, chromosomal deletion or loss of heterozygosity[65]. MRTK is classically associated with RTPS [66]. It is further subdivided into RTPS type 1 and RTPS type 2. RTPS type 1 involves mutation in *SMARCB1* gene whereas RTPS type 2 occurs when mutation occurs in *SMARCA4* gene[8].

Very rarely, its differential diagnosis can be renal medullary carcinoma[65]. Histopathological examination with loss of INI1 marker is diagnostic for MRTK. Imaging studies are not useful[67]. Since, there is no standard treatment established yet, majority of patients are currently treated using intense multimodal regimens that combine early surgical excision of the primary tumor, chemotherapy and local radiotherapy, or high dose chemotherapy followed by autologous stem-cell rescue[68]. These tumors carry a poor prognosis[69].

Clear cell sarcoma of the kidney

It is a rare malignant tumor, generally arising in the renal medulla. Previously, it was also termed as "bone metastasizing renal tumor of childhood" because of its predilection for bony metastasis; but this terminology is no more recommended. Children present with palpable abdominal mass[70]. These tumors are generally diagnosed at 3 years of age. It accounts of 3%-5% of pediatric malignant renal tumors[71]. On microscopy, clear cell sarcoma of the kidney (CCSK) exhibits various patterns. The most common pattern includes classic - characterized by plump ovoid tumor cells with dispersed nuclear chromatin and clear cytoplasm. The tumor cells are arranged in nests or trabeculae and are separated by arborizing fibrovascular septae[72]. Other patterns include myxoid, cellular, epithelioid, spindled, storiform, anaplastic and palisading verocay body[71]. On immunohistochemistry, the tumor cells show dual nuclear positivity for Cyclin D1 and BCOR[73].

The molecular pathology of CCSK includes three mutations[74-76]: *BCOR* ITD exon 15; *BCOR::CCNB3* gene fusion; *YWHAE::NUTM2* gene fusion.

Its differential includes stromal predominant Wilms tumors[2]. Diagnosis is made on histopathology. Imaging study helps to locate origin of tumors. Nephrectomy followed by post operative chemotherapy (doxorubicin) and flank radiation therapy is the treatment administered in CCSK patients[71,77]. Prognosis is variable. Approximately 15% of patients experience relapse[78].

Anaplastic sarcoma of the kidney

Anaplastic sarcoma of the kidney is a rare tumor, usually presenting with a large renal mass[79]. The age range of the patients is 10 months to 41 years. Less than 30 cases are reported in the literature. On microscopy, the tumor has cystic and solid sarcomatous areas. Predominantly, the tumor is comprised of sarcomatous component having tumor cells with large hyperchromatic pleomorphic nuclei; surrounded by cystic component at periphery. Malignant cartilaginous and embryonal rhabdomyosarcoma foci can also be present[80-81]. Two mutation patterns are observed in these tumors, *DICER 1* and RNAaseIIIb mutation[82]. DICER1 syndromic association has been reported[83].

Histopathology is main diagnostic modality. Its closest differential includes anaplastic Wilms tumors, mesenchymal chondrosarcoma and sarcomatoid RCC[81]. Due to very less number of reported cases and lack of follow up of patients; standardized treatment care and prognosis still needs to be determined. However, surgical removal of mass followed by chemotherapy / radiotherapy are being tried. In reported cases, survival rate is around 75%[84,80]. Table 4 outlines the common modes of presentation of paediatric renal tumors.

Renal Ewing sarcoma

It is an extremely rare tumor seen in children and adolescents with median age of diagnosis being 27 years. Patients present with nonspecific symptoms like abdominal pain, mass and haematuria. According to one study, primary renal Ewing sarcoma accounts for 1.5% of all Ewing sarcoma cases[85]. The tumor is characterized by small round blue tumor cells, having round monomorphic nuclei, with fine stippled chromatin, inconspicuous nucleoli and scant clear to eosinophilic cytoplasm. Homer-Wright pseudo rosettes can be seen[86]. On immunohistochemistry, the tumor cells show membranous CD99 and nuclear NKX2.2 expression[87,88].

Table 4 Modes of presentation of paediatric renal tumors

Renal tumor	Presentation
Paediatric cystic nephroma	Palpable abdominal lump[7]
Metanephric adenoma	Asymptomatic to symptomatic (fever, haematuria, abdominal pain and mass), polycythaemia[20]
Metanephric stromal tumor	Abdominal mass, extrarenal vasculopathy, such as bleeding and hypertension[29]
Metanephric adenofibroma	Haematuria and polycythaemia[34]
Ossifying renal tumor of infancy	Haematuria[37]
Mesoblastic nephroma	Abdominal mass[44]
Nephroblastoma (Wilms tumor)	Abdominal mass[54]
Malignant rhabdoid tumor of the kidney	Abdominal mass[63]
Clear cell sarcoma of the kidney	Abdominal mass[70]
Anaplastic sarcoma of the kidney	Large renal mass[79]
Renal Ewing sarcoma	Abdominal pain, mass, hematuria[85]
Renal cell carcinoma with MiT translocations	Asymptomatic to symptomatic abdominal pain and haematuria[92]
ALK-rearranged renal cell carcinomas	Haematuria, abdominal pain or periumbilical pain[96]
Eosinophilic solid and cystic renal cell carcinoma	Asymptomatic[103]
SMARCB1-deficient renal medullary carcinoma	Haematuria, flank or abdominal pain, dysuria, weight loss[107]

Molecularly, two types of translocations are observed in these tumors[89,90]: t(11;22)(q24;q12) resulting in fusion of *EWSR1-FLI1*; seen in 85%-90% cases. t(21;22)(q22;q12) resulting in fusion of *EWSR1-ERG*; seen in 5%-10% cases.

Differential diagnosis can be other small round cell tumors such as blastemal predominant Wilms tumor and neuroblastoma[2]. Histopathological examination with immunohistochemistry and molecular confirmation is diagnostic. Treatment includes chemotherapy, radiotherapy and surgery[91]. Prognosis is poor in patients who present with metastasis at the time of diagnosis[85].

MOLECULARLY DEFINED TUMORS

RCC with MiT translocations

The tumor affects children and young adults. The two types of RCCs that belong to the MiT family includes Xp11 translocation RCC with *TFE3* gene fusions and t(6;11) RCC with *TFEB* gene fusions. *TFE3* rearranged RCCs comprises about 40% of paediatric RCCs whereas *TFEB* rearranged RCCs are comparatively less, having only about 100 cases reported in the literature. Prior exposure to cytotoxic therapy is an important risk factor implicated in these tumors. The presentation ranges from asymptomatic to symptomatic abdominal pain and haematuria. *TFE3* rearranged RCCs exhibit papillary and alveolar growth pattern, having pseudostratified tumor cells with pleomorphic nuclei and clear to eosinophilic cytoplasm. Psammoma bodies may be seen. The tumor cells are nuclear immunopositive for TFE3. *TFEB* rearranged RCCs have biphasic appearance comprising large epithelioid cells and small cells around basement membrane[92].

Both *TFE3* and *TFEB* rearranged RCCs exhibit different molecular pathology. *TFE3* rearranged RCCs include fusion of *TFE3* with other genes like *ASPL*, *PRCC*, *PSF*, *CLTC* and many more[93]. On the other hand, *TFEB* rearranged RCCs displays *MALAT1 (Alpha)::TFEB* fusion[94].

The tumors can be diagnosed on imaging, histopathology, immunohistochemistry and fluorescent in situ hybridization (FISH) analysis. The differential diagnosis includes clear cell RCC, papillary RCC and clear cell papillary RCC. Surgery remains the mainstay treatment for localized tumors including regional nodal metastasis. Immunotherapy and therapies targeting vascular endothelial growth factor receptor are being tried in metastatic cases. Prognosis is variable; prognosis is worse compared to papillary RCC and similar as that of clear cell RCC[95].

ALK-rearranged RCCs

ALK-rearranged RCCs comprises less than 1% of all renal neoplasms. Patients present with haematuria, abdominal pain or periumbilical pain[96]. Patient age ranges from 3 to 85 years. It comprises 3.5%-3.8% of paediatric renal cancers. Microscopically, the tumor cells are infiltrative having vesicular nuclei and small nucleoli. The tumor cells have granular eosinophilic cytoplasm. Mucin pools, lymphoplasmacytic infiltrate and intravascular sickled red blood cells (RBCs) can be found. On immunohistochemistry, the tumor cells are ALK positive. INI1/SMARCB1 is retained in tumor cells[97]. Various fusions with *ALK* gene observed are *VCL-ALK* fusion; associated with sickle cell trait[98]. *TPM3-ALK* fusion; not associated with sickle cell trait[97]. Rarely *STRN-ALK, EML4-ALK, HOOK1-ALK* fusions[96,99].

Diagnosis can be made by ultrasonography and CT scan. On contrast CT scan, a heterogeneous enhancing mass is seen [96]. Its differential diagnosis includes renal medullary carcinoma[100]. For small tumors confined to kidney, radical nephrectomy or nephroureterectomy is preferred. *ALK* targeted inhibitors (alectinib) are tried in metastatic cases. The reported cases have limited follow-up; however dramatic responses has been seen in patients who received *ALK* targeted inhibitors[101].

Eosinophilic solid and cystic RCC

Eosinophilic solid and cystic RCC (ESC-RCC) is a rare and indolent renal tumor that affects female individuals both with and without tuberous sclerosis complex[102]. Around 70 cases are reported in literature. The age of presentation ranges from 14 to 75 years. Patients have mostly asymptomatic presentation[103]. On histopathology, eosinophilic tumor cells are seen arranged in compact nests surrounded by macro and microscopic cysts demonstrating hob nailing pattern of single layered neoplastic cells[104]. On immunohistochemistry, the tumor cells are positive for CK20 and PAX8 whereas negative for CK7 and C-kit[105]. Biallelic somatic mutations of *TSC1* (hamartin) or *TSC2* (tuberin) genes, resulting in upregulation of mTOR pathway are seen in these tumors[106].

Children are generally asymptomatic and the tumor may be discovered incidentally on routine imaging. Its differential diagnosis includes renal oncocytoma and chromophobe RCC. Surgical resection is the treatment of choice. mTOR pathway inhibitors are tried in metastatic cases[103]. Although there is little follow-up data, surgical resection seems to have cured most ESC-RCCs[106].

SMARCB1-deficient renal medullary carcinoma

Patients have broad age of presentation ranging from childhood to old age. This tumor predominantly involves right kidney and is strongly associated with sickle cell trait patients[107-108]. It comprises less than 0.5% of all renal carcinomas. These patients are always almost symptomatic and present with haematuria, flank or abdominal pain, dysuria and weight loss[107]. The tumor cells are arranged in cords, tubules, sheets and nests. The tumor cells have pleomorphic nuclei, vesicular nuclear chromatin, prominent nucleoli and eosinophilic cytoplasm. Sickled RBCs are present[109]. On immunohistochemistry, the tumor cells are PAX8, cytokeratin, EMA and vimentin positive[110]. SMARCB1/INI1 is lost in tumor cells[111]. Chromosomal translocation or deletion leading to inactivation of *SMARCB1* gene are seen in these cases[112].

Histopathology along with immunohistochemistry demonstrating infiltrating high-grade adenocarcinoma with SMARCB1 loss is diagnostic. Its differential diagnosis includes *VCL::ALK* fusion RCC[100]. Treatment includes radical nephrectomy and chemotherapy administering platinum-based regimens[113]. Prognosis is poor. Most patients present with nodal or liver / lung metastasis at the time of diagnosis[114].

ROLE OF ULTRASOUND GUIDED RENAL MASS BIOPSY

Diagnosis of renal masses can be made safely and accurately using ultrasound guided method which has low rate of non-diagnostic outcome and complications[115]. Apart from routine histopathology and immunohistochemistry, the biopsy can also be utilized for molecular characterization and ancillary techniques. FISH analysis, chromosomal study, microarray technique for understanding gene expression profiling of renal tumors can also be performed[116].

CONCLUSION

This review article summarizes the spectrum of paediatric renal tumors. Every tumor has its own unique histomorphology, immunohistochemistry and molecular pathology. Histopathology followed by immunohistochemistry is always the gold standard for definitive diagnoses of these tumors. Certain tumors have association with genetic syndromes, which makes it prognostically more challenging for children. Thus, management goal should always be early diagnosis of these tumors.

FOOTNOTES

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MINIREVIEWS

Anti-neutrophil cytoplasmic antibody-associated vasculitis and kidney cancer: A mini review

Samuel Wilding, Henry H L Wu, Nina Brown, Rajkumar Chinnadurai

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Abstract

This mini review explores the links between anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) and kidney cancer. Several studies suggest an increased incidence of cancer for patients with AAV. Different cancer types have shown different standardized incidence ratios (SIRs) in association with AAV. The SIRs of kidney cancer were found to be between 1.7 and 3.3 as per three retrospective data analyses. This association is likely multifactorial, with increased de novo cancer risks associated with inflammatory diseases; carcinogenic therapies such as cyclophosphamide; and reduced immune surveillance of neoplastic cells in immunocompromised individuals. Some studies have proposed that cancers, including kidney cancer, could be a potential trigger for AAV. Due to variability in SIRs and a lack of multicenter studies looking specifically into the incidence of kidney cancer at AAV diagnosis and on follow-up post initiation of AAV treatment, there remains a lack of evidence to support formal screening for kidney cancer in the AAV patient cohort. Greater awareness on the increased risk of cancer in AAV patients, prompt urological assessment of "red flag" symptoms of kidney cancer, and smoking cessation advice to reduce cancer risk should be standard of care for patients with AAV.

Key Words: Anti-neutrophil cytoplasmic antibody-associated vasculitis; Kidney cancer; Etiology; Pathophysiology; Immunosuppression

Core Tip: There are numerous etiologies proposed which may explain for the associations between anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) and kidney cancer, such as immunosuppressive agents prescribed for treatment of AAV leading to increased kidney cancer risk. Nevertheless, there remains variability in published incidence rates and a lack of high-quality multi-center studies looking specifically into the incidence of kidney cancer at AAV diagnosis and on follow-up post-initiation of AAV treatment. A greater clinical awareness of the increased risk of cancer in AAV patients is needed, to promote prompt urological assessment and promote risk reduction measures in this patient population.

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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a heterogenous group of inflammatory conditions that mainly affects small blood vessels and is often associated with autoantibodies targeted at proteinase 3 (PR3) or myeloperoxidase (MPO)[1]. AAV is associated with excess morbidity and premature death, with a previous study reporting all-cause mortality of approximately 38% at 7-year follow-up[2].

Mortality and morbidity outcomes in AAV continue to improve over time with advances in immunosuppressive treatment regimen. Nevertheless, both treatment and disease are associated with substantial morbidity, necessitating vigilance for complications including treatment-related cancer risks[3].

Despite improvements in morbidity and mortality, there are ongoing etiological uncertainties with AAV. Associations between cancer and AAV have been well-established, with past studies demonstrating increased risks of immunosuppression related non-melanoma skin cancer and cyclophosphamide-associated bladder cancer[4]. However, there are numerous studies that have also shown an association between AAV and other solid tumors including kidney cancer[5-7]. This suggests a potential alternative relationship including malignancy as a disease triggering factor for AAV or conversely, AAV arising as a paraneoplastic syndrome[8].

In this mini review, we aimed to specifically assess the epidemiological links between AAV and kidney cancer as this had not been specifically addressed on previous reviews. We also aimed to explore potential pathophysiological links between the two diseases and their management. Finally, we aimed to utilize that information to assess if changes to the assessment for kidney cancer were indicated *via* a specific screening tool.

A comprehensive search of the National Library of Medicine database *via* PubMed was performed in March 2024 to identify studies examining the relationship between AAV and kidney cancer. The search strategy included the terms: (kidney cancer OR renal cancer OR malignancy) AND (vasculitis OR AAV). To expand our review, the reference lists of relevant articles were manually examined, and additional targeted searches were conducted to address any gaps identified in the initial search. Only English-language publications were considered. Out of 118 search results, 37 articles were included based on a review of suitability based on their abstracts.

EPIDEMIOLOGY OF CONCURRENT AAV AND KIDNEY CANCER

Previous studies have evaluated the incidence of malignancy in patients with AAV which observed varied, but elevated standardized incidence ratios (SIRs) of all-site solid tumors when compared to the general population – as high as 2.4 as per one study by Knight *et al*[9], which is noted to be twice the SIRs of the general population and to be equivalent to the SIRs for any cancer post-kidney transplantation after excluding non-melanoma skin cancer (*i.e.* 2.4)[10]. SIRs are the ratio of incident cases in a cohort to the incident cases that would be expected, for example, incidence rates in the general population *vs* those in patients with AAV as in this case. Another study demonstrated cumulative overall cancer incidence of 8% at 5-year follow-up and 13% at 8-year follow-up for patients diagnosed with AAV which is significantly higher than those without the condition[11]. Furthermore, the annual incidence rate of urological malignancies was noted to be 0.37% in a cohort of patients with all-cause chronic kidney disease[12].

Most of the studies demonstrate a more significant association between malignancy and PR3 AAV in comparison to malignancy and MPO AAV. This is possibly due to the typically relapsing remitting course of PR3 AAV requiring higher cumulative doses of immunosuppression or higher mortality associated with MPO AAV[11]. It has also been proposed that incidental findings of non-invasive tumors identified during initial diagnosis and follow-up for patients with AAV may also contribute to an increase in reported incidence of kidney cancer in this cohort.

There were no dedicated studies which looked specifically at the incidence of kidney cancer in patients with AAV. However, the SIR of kidney cancer was reported to be between 1.7 and 3.3 as per three retrospective data analyses evaluating the incidence of various cancer types in patients with AAV[6,13].

Two case studies reported AAV presentations alongside the presence of detectable kidney masses which were later confirmed to be renal cell carcinoma, one appearing in a 61-year-old male patient and the other in a 72-year old female patient[14]. Unfortunately, no further demographic data were included in these case reports and we have identified no studies which conveyed demographic details of patients presenting concurrently with AAV and kidney cancer or those who developed kidney cancer following AAV treatment.

ETIOLOGICAL AND PATHOPHYSIOLOGICAL INTERLINKS BETWEEN AAV AND KIDNEY CANCER

AAV as a consequence of kidney cancer

The pathophysiology of AAV remains unclear, and multiple triggering factors have been proposed, including malignancy. Tatsis *et al*[15] performed a retrospective statistical analysis on 956 patients, 477 with PR3 vasculitis and 479 patients with rheumatoid arthritis in a control group. The investigators reported a statistically significant increased incidence of renal cell carcinoma in the PR3 vasculitis group (P = 0.0464) with an odds ratio of 8.7 compared to the control group. Of the 7 patients with PR3 vasculitis and renal cell carcinoma, 5 patients simultaneously presented with both conditions. However, PR3 antibodies were not found in malignant tissues obtained from the PR3 group[15]. The number of contemporaneous presentations calls into question the nature of this link-could AAV potentially arise as consequence of malignancy?

There have been multiple case reports of presentations of vasculitis including AAV as a paraneoplastic syndrome[16-19]. Solans-Laqué *et al*[20] identified 144 cases of patients with coexistent vasculitis and solid tumors, with renal cell carcinoma the second most commonly associated solid tumor behind non-small cell lung cancer (n = 20). Tsimafeyeu *et al*[17] noted an 8% incidence rate of paraneoplastic vasculitis in patients with metastatic kidney cancer, particularly leukocytoclastic vasculitis on the lower extremities which were confirmed on skin punch biopsy. Fibrin deposits and tumor antigen-antibody immune complexes were identified in the vascular wall on biopsy. Cross-reactivity between the antigens of the tumor and the cell surface proteins on the endothelial cell, and subsequent development of inflammation and necrosis could be a mechanism whereby malignancy leads to vasculitis in a paraneoplastic syndrome.

In a review of individuals with paraneoplastic vasculitis in those diagnosed with solid tumors, Solans-Laqué *et al*[20] reported an 1.2% incidence of concurrent presentation of AAV and malignancy in patients diagnosed with both conditions throughout their prospective follow-up period (1 in 86 patients with both malignancy and AAV). Concurrent presentation with cutaneous leukocytoclastic vasculitis was significantly more frequent (9 out of 15 cases presenting with concurrent vasculitis and malignancy) compared to other forms of vasculitis. After therapy for the underlying malignancy, most patients in this cohort had a complete resolution of their vasculitis, which further supports a paraneoplastic relationship between AAV and malignancy[20].

Pankhurst *et al*[21] performed a retrospective review of 200 consecutive patients with AAV and identified 20 patients (14 with microscopic polyangiitis and 6 with granulomatosis with polyangiitis) who had a malignancy but with only 4 within this 200-patient cohort having a concurrent diagnosis of both malignancy and AAV. In the remaining cases, malignancy predated vasculitis by a median duration of 96 months, and there was no evidence suggestive of subsequent malignancy relapse following development of vasculitis which would have supported a paraneoplastic etiology of the vasculitis.

Predisposition of patients in an inflammatory state towards kidney cancer

This relationship can be evaluated conversely, to examine whether AAV could lead to the development of de novo malignancy. It has been well established that systemic chronic inflammatory conditions such as systemic lupus erythematosus and systemic sclerosis are associated with an increased overall cancer risk[22,23]. Localized chronic immune activation increases risk of malignancy in a variety of body systems. There is an increased colorectal cancer risk for patients with inflammatory bowel disease, with one study demonstrating a 7% colorectal cancer risk after 30 years which has necessitated screening colonoscopies in this patient group[24]. Hemminki *et al*[25] assessed the risk of lung cancer across 12 autoimmune diseases and found increased SIRs in all 12. However, those autoimmune conditions reported with a SIR greater than 2.0 were those known to present with lung manifestations. This suggests that although both systematic and local inflammatory autoimmune processes resulted in an increased risk of cancer, local inflammation displayed closer associations with de novo cancer risk. It is therefore plausible that chronic inflammation and necrosis at the kidney cancer cell surface secondary to the immune response to tumor antigens could predispose to vasculitis.

As noted previously, the SIR of kidney cancer in patients with AAV was reported to be between 1.7 and 3.3. However, these studies have not published a timeline of diagnosis of the two conditions in the patient groups they reviewed which limits our ability to pick apart this relationship. They have also not distinguished between PR3 and MPO AAV and their respective risks towards kidney cancer incidence. Going forward, it would be useful to evaluate this unknown to assess if an increased relapse rate in PR3 AAV may lead to an increase in kidney cancer risk[11]. This may become increasingly relevant as morbidity and mortality outcomes improve through advances in treatment and with time, the longer-term consequences for patients living with AAV are being observed.

Figure 1 summarizes the plausible etiological and pathophysiological relationship that links AAV and kidney cancer as both a potential trigger and consequence, based on current evidence as discussed in the section above.

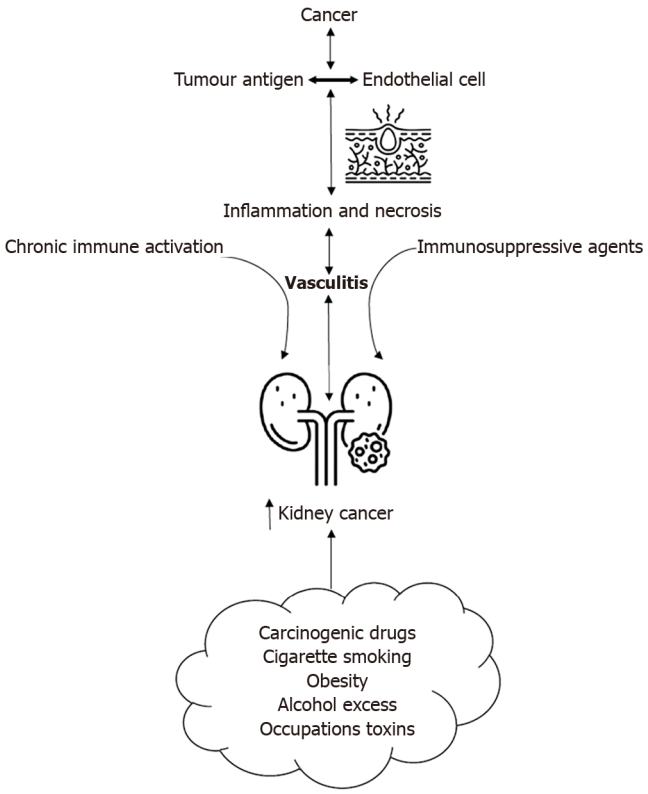

Figure 1 Plausible etiological and pathophysiological interlinks between anti-neutrophil cytoplasmic antibody-associated vasculitis and kidney cancer.

CONSIDERING THE ROLE OF CARCINOGENIC AND IMMUNOSUPPRESSIVE TREATMENT IN AAV LEADING TO INCREASED CANCER RISK

Immunosuppressive agents have well-recognized carcinogenic properties, particularly cyclophosphamide, which has been linked to urinary tract cancer with risks increasing with higher cumulative doses such as those administered in patients treated for AAV[26]. This has been particularly highlighted in the study by Sánchez Álamo *et al*[27], in which much higher cumulative cyclophosphamide doses were used (in comparison to that from the post-CYCLOPS EULAR studies[28]), which was associated with significant increased risks of urological tract cancer. It has also been shown that concomitant use of Cyclophosphamide and Etanercept further increases this risk, with patients receiving both medications having an SIR for solid malignancy of 3.8 compared to 1.7 in those patients not receiving Etanercept[29]. However, Etanercept is not routinely used in the treatment of AAV. Azathioprine, Methotrexate and Rituximab have also been associated with an increased malignancy risk, though these agents have not been specifically linked with kidney cancer[30-32].

It is well-known immunosuppressive drug regimens carry an association with renal cell carcinoma in kidney transplant recipients[33,34]. Kidney transplant recipients have been shown to be at a 5-to-10-fold increased risk of developing renal cell carcinoma, particularly within the native kidneys, which make up 90% of all cases of renal cell carcinoma in transplant recipients[35,36]. The development of renal cell carcinoma in kidney transplant recipients has a multifactorial etiology, with a major cause being the malignant transformation of renal cysts which were already present when patients were receiving dialysis[35,36]. Despite this demonstrated elevated risk of malignancy, screening for renal cell carcinoma in kidney transplant recipients has not yet been proven to be cost-effective[37].

In addition to the carcinogenic risk of immunosuppressive drugs, immunosuppression in-itself is associated with an increased risk of kidney cancer. In a human immunodeficiency virus (HIV)-positive population, there is an 8.5-fold greater chance of developing renal cell carcinoma than the general population, with renal cell carcinoma typically presenting around 15 years earlier compared to the non-HIV affected general population[38]. This is likely due to reduced immune surveillance in immunocompromised individuals. Nevertheless, the risk of development of renal cell carcinoma directly secondary to HIV viral activity and host response cannot be excluded as well.

SCREENING FOR CONCURRENT AAV AND KIDNEY CANCER IN THE CLINICAL SETTING

From the evidence presented in this mini review, we advocate a perspective to encourage increased awareness of the potential associations that lie between kidney cancer and AAV. Considering the potential of malignancies including

kidney cancer being a potential trigger for AAV should prompt screening for red-flag symptoms of malignancy, which includes observing a palpable kidney mass or abnormal renal imaging and visible hematuria during patient examination. The appearance of cutaneous vasculitic rash should also raise concerns of vasculitis presenting as a paraneoplastic syndrome.

During the ongoing maintenance phase of immunosuppression treatment, clinicians should be aware of patients having an increased risk of malignancies secondary to chronic immune activation, carcinogenic drugs and immunosuppressive effects impacting tumor surveillance. Risk of kidney malignancy is likely to increase further with the presence of established risk factors including cigarette smoking, obesity, hypertension, alcohol excess and occupational exposure such as trichloroethylene[39].

Akin to kidney transplant recipients, routine formal screening for kidney cancer in patients with AAV is unlikely to be a cost-effective strategy. However, due to the increased incidence of kidney cancer in this patient group, prompt investigation of potential kidney cancer-related symptoms, particularly in patients with known associated risk factors, should be considered as standard practice. In-office ultrasonography examination could be considered an effective, low-cost screening tool given the low incidence of AAV and potentially significant benefits for morbidity and mortality for patients of early detection of potential kidney malignancy.

The presence of new-onset microscopic hematuria should not only provoke the search for evidence of disease activity, but also to exclude potential renal tract malignancy.

LIMITATIONS AND REVIEW OF EVIDENCE

There are limitations placed on the scope of this review given the paucity of published evidence. There are no multi-center studies assessing the incidence of kidney cancer at presentation or at different timeframes from diagnosis hence the inability to make firm recommendations. In addition to this, the assessment of incidence was completed through retrospective data analysis which comes with inherent limitations such as missing data, selection bias and confounding variables. This method of research also comes with the inherent risk of skewed data due to publication bias which may highlight positive findings or unusual presentations such as the multiple case reports of co-presentation with AAV and kidney cancer, in which the actual incidence of this may be incredibly low. There was also notable heterogenicity in study designs when comparing incidence rates, contributing to the variability in reported SIRs. We would recommend further multi-center prospective studies assessing the incidence of the breadth of malignancies at and following diagnosis with AAV and the timeframes and therapies used in these cases, which would help further elucidate the relationship between AAV, cancer and immunosuppression.

CONCLUSION

As clinical outcomes improve for patients treated for AAV with advancements in available treatment options, the long-term sequelae of both the disease and its treatments are of increasing importance. The incidence of kidney cancer is higher in patients living with AAV compared to the general population, which may be the result of chronic immune activation or immunosuppression exposure. Therefore, awareness of red-flag symptoms and other risk factors related to kidney cancer are of increasing importance for clinicians involved in the long-term management of this patient population. As the incidence rate of kidney cancer in this patient group remains uncertain, a formal population-level screening approach for kidney cancer for patients with AAV would be unlikely to meet the criteria for a successful screening tool. For now, in clinical practice, a lower threshold for in-office ultrasound assessment or urgent urological assessment, particularly in patients with other risk factors for kidney cancer, should be considered when signs or symptoms of kidney cancer are present in patients with AAV.

FOOTNOTES

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Abstract

Ultrasound has long been an essential tool in nephrology, traditionally used for procedures like vascular access and kidney biopsies. Point-of-care ultrasonography (POCUS), a rapidly evolving bedside technology, is now gaining momentum in nephrology by providing real-time imaging to enhance physical examination findings. Unlike comprehensive radiology-performed ultrasound, POCUS focuses on specific clinical questions, providing immediate and actionable insights. This narrative review examines the philosophy behind POCUS, its expanding applications in nephrology, and its impact on patient care, including its role in diagnosing obstructive uropathy, guiding fluid management, and evaluating hemodynamics in cardiorenal syndrome. Additionally, the review addresses barriers to widespread adoption, such as the need for structured training, competency validation, and interdisciplinary cooperation. By integrating POCUS into routine practice, nephrologists can refine diagnostic accuracy, improve patient outcomes, and strengthen the role of bedside medicine.

Key Words: Point-of-care ultrasonography; Nephrology; Fluid management; Hemodynamic assessment; Competency assessment; Bedside diagnostics

Core Tip: Point-of-care ultrasonography (POCUS) holds transformative potential in nephrology by enhancing diagnostic accuracy and guiding the management of complex hemodynamic derangements, which often overlap with conditions that nephrologists are consulted for, such as acute kidney injury, renal replacement therapy, and electrolyte disorders. Unlike traditional imaging, POCUS provides real-time, bedside insights that enhance clinical decision-making. However, widespread adoption requires structured training, competency validation, and collaboration with other specialties. Overcoming these barriers will help integrate POCUS into routine nephrology practice, ultimately improving patient care and outcomes.

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INTRODUCTION

Ultrasound has been an important imaging tool in nephrology since the specialty's early days. Traditionally, it has been used to guide procedures such as hemodialysis catheter placement and kidney biopsies, as well as to assess kidney morphology[1]. In certain countries and regions, nephrologists are also responsible for hemodialysis vascular access care, where Doppler ultrasound plays a crucial role in both planning access placement and managing vascular access dysfunction[2]. Point-of-care ultrasonography (POCUS) is an emerging bedside tool in nephrology, intended to complement physical examination findings with real-time ultrasound information. Unlike a comprehensive examination performed by the radiology department, POCUS is used to address focused clinical questions and is typically performed by the physician who is directly taking care of the patient[3,4]. The widespread availability of ultrasound equipment, especially hand-held and portable cart-based machines, along with the pioneering efforts of physicians in emergency medicine, has significantly contributed to the growing popularity of POCUS and the recognition of its clinical value across various specialties, including nephrology[4,5]. This narrative review aims to discuss the philosophy behind POCUS and highlight its applications and benefits in nephrology as well as common misconceptions and challenges for further advancements and mass adoption.

THE PHYSICAL EXAM: AN ART IN NEED OF A MODERN TOUCH

While it's true that physical exam skills may be diminishing, especially among younger doctors[6,7], clinicians also frequently overestimate the diagnostic accuracy of traditional physical exam findings[8]. Although methodical history-taking and physical exams remain valuable, many of the so-called 'classic signs' were identified during a time when effective treatments were unavailable, and 'late-stage' disease presentations were the norm. As a result, most classic signs and symptoms tend to lack sensitivity, though some may be quite specific[6]. Even with Laennec's revolutionary invention of the stethoscope which went on to become the symbol of the medical profession, many auscultation findings face the same issue: A recent meta-analysis on the diagnostic accuracy of lung auscultation for common acute pulmonary conditions like congestive heart failure, pneumothorax, or obstructive lung disease found an overall sensitivity of just 0.37, although specificity remained high at 0.89[9]. Even seasoned cardiologists often struggle with the low sensitivity of cardiac auscultation for detecting valvular heart disease, a condition usually identified by cardiac murmurs[10].

Physical exam also proves inadequate for hemodynamic assessment, often referred to as 'volume status assessment', which is a vital skill for nephrologists. Studies dating back over thirty years have consistently highlighted this issue. For instance, clinical evaluation showed less than 50% accuracy in diagnosing extracellular fluid volume depletion as the cause of hyponatremia in a study involving non-edematous patients[11]. On similar lines, in a population of heart failure patients, where filling pressures were invasively determined, 44% of patients with pulmonary capillary wedge pressures ≥ 22 mmHg did not have evidence of clinical congestion (rales, peripheral edema and/or elevated jugular venous pressure)[12]. Likewise, lung crackles, whether alone or combined with peripheral edema, have been shown to poorly reflect interstitial lung edema in end-stage renal disease patients when compared to lung ultrasound (LUS)[13]. It's imperative that we need better tools for the hemodynamic evaluation of the increasingly complex patients we encounter in our daily practice.

POCUS: UNDERSTANDING THE RATIONALE AND RECOGNIZING ITS POTENTIAL

POCUS involves the acquisition, interpretation, and immediate clinical integration of ultrasonographic imaging performed by the treating clinician at the patient's bedside[4]. It is often described as the 5th pillar of physical examination in addition to inspection, auscultation, percussion, and palpation[14]. Although commonly misunderstood, POCUS is not intended to replace comprehensive diagnostic ultrasounds performed by radiologists or cardiologists, nor is it a

substitute for imaging techniques like computed tomography scans. Instead, it enhances the sensitivity of the traditional physical exam, allowing clinicians to answer specific questions at the bedside[4,5]. That said, in certain scenarios, POCUS may reduce the need for additional diagnostic tests, potentially lowering healthcare costs when focused questions are adequately addressed. Indeed, POCUS should NOT be performed without a focused clinical question in mind[15]. Examples of such questions include: "Is obstructive uropathy the cause of acute kidney injury in this patient?", "Why is my patient hypotensive during dialysis?" or "Is pulmonary edema the cause of the dyspnea of my patient?".

It has been reported that even medical students with limited POCUS training have better diagnostic accuracy with hand-held ultrasound than physical exam performed by senior cardiologists for common cardiac pathologies[16]. Remarkably, ultrasound has over 90% sensitivity and specificity for the diagnosis of commonly encountered pathologies such as pulmonary edema, pleural effusion, or left ventricular (LV) dysfunction[4,17], a substantial improvement compared to conventional physical exam alone. These findings are very relevant for nephrologists who must use this information for clinical decision-making such as diuretic therapy titration or ultrafiltration orders. It must be emphasized that POCUS's utility is not limited to diagnosis. This tool is also very useful for evaluating the response to therapeutic interventions such as fluid therapy or ultrafiltration by monitoring dynamic sonographic parameters[18]. Furthermore, POCUS enables clinicians to perform advanced hemodynamic assessments, such as evaluating LV filling pressures or detecting end-organ dysfunction from congestion, provided the user has appropriate training[19].

All of these characteristics facilitate real-time decision-making at the bedside, reducing fragmentation of care, allowing clinicians to order fewer tests, and being more efficient and confident in their management of the patient[20,21]. Indeed, contrary to most technological advances in medicine, POCUS is a tool that puts the clinician back at the bedside and at the same time, improves patient satisfaction[22]. It is important to remember that clinical judgment must always guide decision-making. As the saying goes, 'a fool with a stethoscope will remain a fool with an ultrasound'. POCUS users should be mindful of the cognitive biases, such as the steep curve of the Dunning-Kruger effect where less experienced users may feel more confident than experts due to their inability to recognize their own limitations[23]. They should also avoid making decisions based on a single finding and instead perform multi-organ assessments to minimize the risk of confounding[19,24]. Additionally, POCUS users must recognize when a more comprehensive evaluation is necessary, for example, a consultative echocardiogram for complex valvular disorders.

CLINICAL APPLICATIONS OF POCUS IN NEPHROLOGY

While it may appear that POCUS is only useful for acute or critical care patients, this couldn't be further from the truth. POCUS usefulness is ubiquitous across the entire clinical landscape of nephrology (Figure 1). In hemodialysis patients, it can be used to titrate dry weight or evaluate causes of hypotension during dialysis[25,26]. It can also be used to troubleshoot vascular access problems, such as helping dialysis staff with cannulation, assessing fistula maturation, or differentiating hematomas from other causes of tumefaction[27]. Additionally, in peritoneal dialysis patients, POCUS aids in diagnosing and differentiating between types of catheter-related infections (*e.g.*, exit-site *vs* tunnel infection) and in monitoring the treatment response[28,29]. After a kidney transplant, POCUS can be used to assess graft perfusion and exclude vascular thrombosis, especially in cases of delayed graft function and/or if a comprehensive Doppler ultrasound by radiology is not immediately available[15]. Additionally, hemodynamic assessment is one of the most challenging aspects of nephrology, where POCUS excels. Multi-organ ultrasound, including that of the lungs, kidneys, heart, and Doppler interrogation of systemic veins, is valuable in evaluating "prerenal" (more precisely "hemodynamic") acute kidney injury and managing cardiorenal patients. We will briefly discuss each component with a focus on practical applications.

LUS

Traditionally, LUS was considered impossible due to air scattering ultrasound waves, hindering the evaluation of underlying tissues. This notion was challenged in the 1990s by Lichtenstein[30], a French critical care physician, who pioneered point-of-care LUS and demonstrated the clinical value of various ultrasound artifacts generated by air and its interaction with lung water. An intriguing aspect of LUS is that it primarily relies on these artifacts rather than direct anatomical imaging, meaning most images lack a direct clinical-anatomical correlation (except when the lung is consolidated/hepatized). Therefore, the selected imaging preset should have all image-enhancing software, such as harmonics, turned off to ensure that ultrasound artifacts are not reduced or eliminated[25]. LUS is associated with various patterns and signs, with the most clinically relevant ones included in the Bedside LUS in Emergency protocol. This clinical algorithm helps manage critical care patients with dyspnea, demonstrating that common conditions like pneumothorax and pneumonia can be rapidly diagnosed using LUS[31].

For nephrologists, mastering LUS is crucial as it is highly sensitive in detecting tissue congestion, including cardiogenic pulmonary edema and pleural effusion[32]. The learning curve is relatively shallow, images are straightforward to acquire, it is highly reproducible across physicians[33], and it can be performed quickly in any setting with (almost) any ultrasound device[30]. Normal lung ultrasonography is characterized by the presence of pleural sliding, which is the movement of the visceral pleura over the parietal pleura, and horizontal A-lines (Figure 2A). These A-lines are a reverberation artifact originating from the pleural line, indicating a normally aerated lung. Pleural effusion is typically identified in the thoracic posterolateral region of a supine patient by detecting an anechoic (black) effusion in the pleural space[30] (Figure 2B). Additionally, LUS can be used to estimate the volume of the effusion[34].

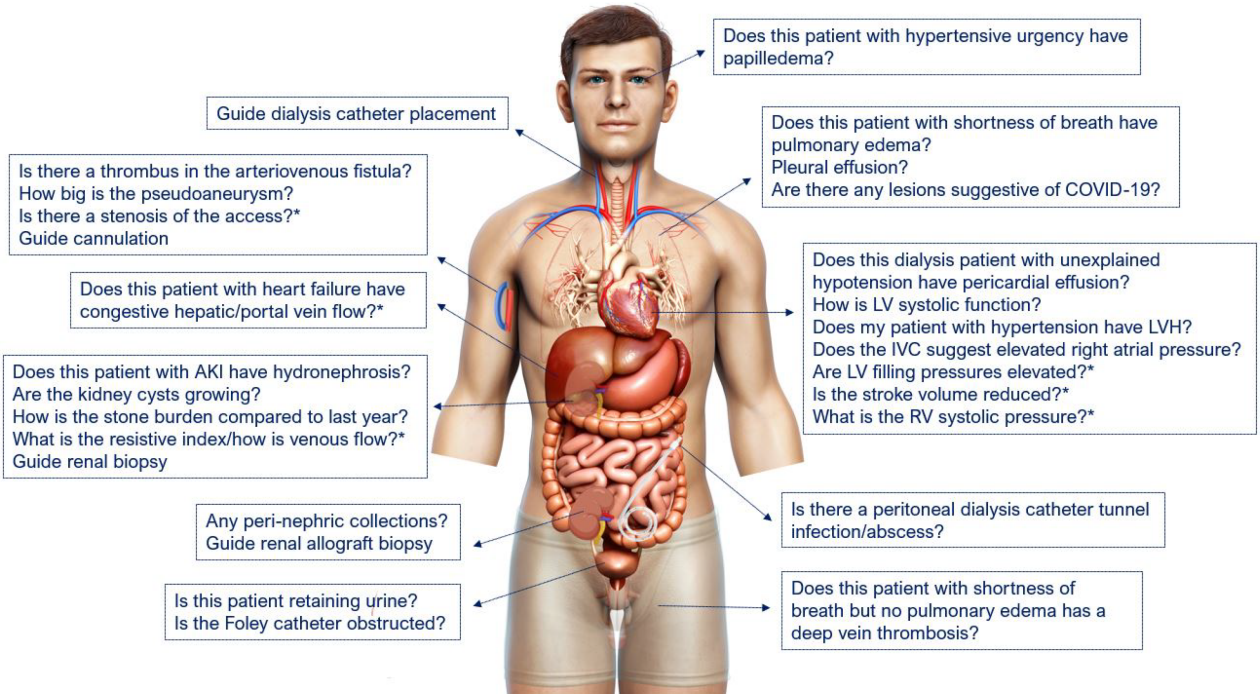

Figure 1 Point-of-care ultrasonography use-cases in nephrology. Some examples of nephrology-related clinical questions that can be answered using point-of-care ultrasonography. The asterisk indicates advanced sonographic applications requiring a higher operator skill level/additional training. Reproduced from Koratala *et al*[58]. COVID-19: Coronavirus disease 2019; LV: Left ventricle; LVH: Left ventricular hypertrophy; IVC: Inferior vena cava; RV: Right ventricle; AKI: Acute kidney injury. Citation: Koratala A, Reisinger N. POCUS for Nephrologists: Basic Principles and a General Approach. *Kidney360* 2021; 2: 1660-1668. Copyright © 2021 by the American Society of Nephrology. Published by Wolters Kluwer Health, Inc. The authors have obtained the permission for figure using (Supplementary material).

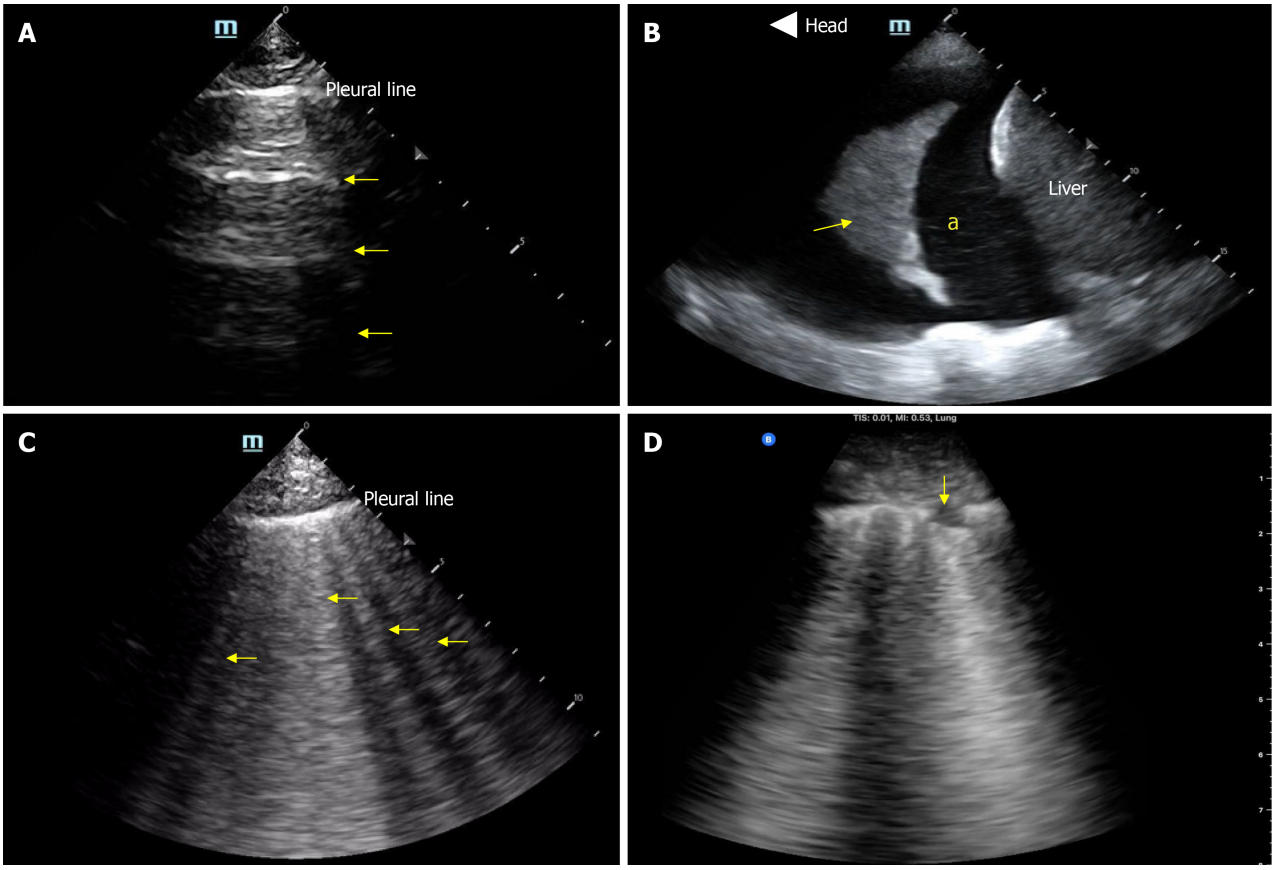

Figure 2 Basic lung ultrasound findings. A: Normal lung ultrasound demonstrating A-lines (horizontal hyperechoic artifacts); B: Pleural effusion ("a")

appearing as an anechoic area above the liver. Arrow points to atelectatic lung; C: B-lines-vertical hyperechoic artifacts emerging from the pleural line indicative of interstitial thickening (typically from fluid); D: Interstitial pneumonia with confluent B-lines and an irregular pleural line. Arrow points to subpleural consolidation.

Ultrasound B-lines, which appear as vertical hyperechoic lines, are ringdown artifacts originating from the pleural line and move with lung sliding[35]. They occur when the interlobular septa and surrounding tissue thicken or become fluid-filled, making them highly sensitive indicators of interstitial syndrome or pulmonary edema[36]. B-lines correlate semi-quantitatively with the amount of extravascular lung water[32] and are a reliable marker of increased LV filling pressures [37]. Typically, B-lines extend from the pleural line to the end of the screen, erasing A-lines or making them less prominent[38] (Figure 2C). Several LUS protocols have been designed to detect pulmonary edema, varying in the number of scanning zones used. Clinically, the presence of two or more positive zones - defined as three or more B-lines per intercostal space - on both sides is strongly indicative of interstitial syndrome[39]. Of note, B-lines are not exclusive to cardiogenic pulmonary edema; they can also be observed in conditions such as interstitial pneumonia, lung fibrosis, and alveolar hemorrhage. Figure 2D illustrates an image from a patient with COVID-19 pneumonia, showing confluent B-lines (fused together) and an irregular pleural line with subpleural consolidation. In contrast, cardiogenic pulmonary edema in a patient without parenchymal lung disease typically presents with a regular-appearing pleural line. A clinical trial tested a LUS-guided treatment strategy in high cardiovascular-risk hemodialysis patients and found that it effectively relieved lung congestion, reduced the risk of repeated hospitalizations for decompensated heart failure, and resulted in less intradialytic hypotension[37].

FOCUSED CARDIAC ULTRASOUND

The interaction between the heart and kidneys is well established, with nephrologists playing a key role in managing cardiorenal syndrome, given the rising prevalence of both cardiovascular disease and chronic kidney disease (CKD). While hemodynamic factors clearly explain the impact of acute dysfunction in one organ on the other, non-hemodynamic factors like neurohumoral overactivation and inflammatory pathways also contribute to chronic injury in both organs and are integral to the pathophysiology of this syndrome[40]. Cardiovascular disorders, including heart failure, atherosclerotic coronary artery disease, and valvular disorders, are highly prevalent in CKD patients[41,42]. Conversely, patients with heart failure are at increased risk for kidney injury, particularly in acute settings[43]. As such, focused cardiac ultrasound (FoCUS) can be a valuable adjunct for nephrologists in day-to-day practice. It enables bedside evaluation of key morphologic and functional parameters that can significantly impact the management of a patient's clinical condition.

Basic FoCUS can help answer common focused questions such as: 'Does the patient have LV systolic dysfunction?', 'Is there right ventricular (RV) dysfunction?', or 'Is there a pericardial effusion?'. Figure 3 illustrates the basic cardiac views. An LV ejection fraction < 50% is the hallmark of heart failure with reduced ejection fraction, a relatively common comorbidity in CKD patients and the elderly[44,45]. Assessing cardiac pump function can help figure out the potential cause of acute kidney injury in acute decompensated heart failure or intradialytic hypotension in chronic hemodialysis patients. It's relatively straightforward since it relies on qualitative LV function assessment and not precise measurements. By observing endocardial movement, mitral valve leaflet excursion, and myocardial thickness, LV systolic function can be visually estimated and categorized as hyperdynamic, normal, reduced, or severely reduced[46].

Many heart failure patients have preserved ejection fraction, where the primary issue lies in elevated filling pressures on both sides of the heart. This results in pulmonary and venous congestion, affecting abdominal organs, including the kidneys [see venous excess ultrasound (VExUS) section]. In this context, assessing RV size and function alongside inferior vena cava (IVC) diameter and collapsibility provides valuable insights. Notably, RV dilation and dysfunction are not exclusive to volume overload. For instance, in patients with acute dyspnea, RV dysfunction may signal a massive pulmonary embolism requiring urgent thrombolysis. In such cases, nephrologists performing POCUS can also detect deep vein thrombosis in the lower extremity. For patients with subacute peripheral congestion and RV dysfunction, more aggressive diuresis may be necessary. However, in conditions such as chronic pulmonary hypertension with tricuspid regurgitation, achieving a "normal" RV size or IVC diameter may be neither feasible nor desirable. Multiple views should be utilized to minimize bias, comparing the RV to the LV and assessing septal motion. Similar to LV evaluation, a qualitative approach is effective for estimating RV function[46]. Ultimately, POCUS must always be interpreted in the appropriate clinical context, as the same finding can have different management implications.

The reported prevalence of pericardial effusion in CKD patients varies significantly, ranging from 2% to 62% in the literature. This condition may arise due to the accumulation of uremic toxins or insufficient dialysis leading to generalized fluid overload[47]. While it may cause chest pain, most patients with low-volume or slowly developing effusions are asymptomatic, and physical signs are often insensitive. However, rapid accumulation, such as from hemorrhage, can lead to cardiac tamponade even if the size is small. If a nephrologist can diagnose pericardial effusion early, appropriate interventions can be implemented - patients with advanced CKD can start dialysis, chronic hemodialysis patients can adjust their dialysis prescription to increase ultrafiltration and efficacy, and anticoagulation may be paused to prevent cardiac tamponade[48]. A recent study demonstrated that FoCUS, when performed by non-cardiologists, achieved excellent diagnostic accuracy (> 95%) in detecting left and RV systolic dysfunction, as well as pericardial effusion[49]. Like other aspects of POCUS, FoCUS should be used to answer specific clinical questions, and its findings must be interpreted within the patient's clinical context, alongside physical exam results, biochemical markers,

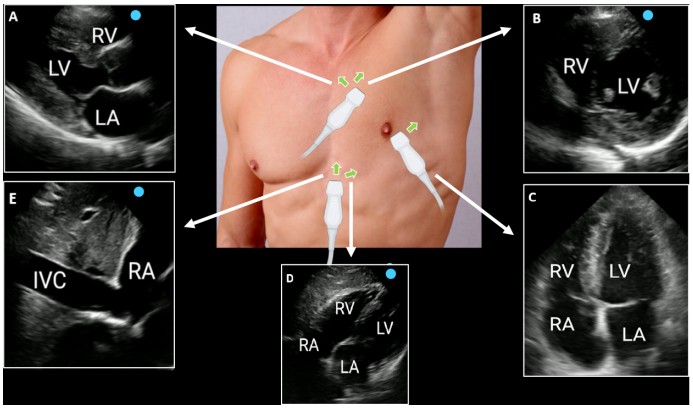

Figure 3 Focused cardiac ultrasound views. A: Parasternal long axis; B: parasternal short axis; C: Apical four-chamber; D: Subxiphoid; E: Inferior vena cava. Green arrows indicate the direction of the transducer orientation marker. Reproduced from Argaiz *et al*[59]. IVC: Inferior vena cava; LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle. Citation: Argaiz ER, Koratala A, Reisinger N. Comprehensive Assessment of Fluid Status by Point-of-Care Ultrasonography. *Kidney360* 2021; 2: 1326-1338. Copyright © 2021 by the American Society of Nephrology. Published by Wolters Kluwer Health, Inc. The authors have obtained the permission for figure using (Supplementary material).

and other sonographic findings. The goal is not to replace comprehensive echocardiography performed by cardiologists; any significant finding that needs further evaluation or uncertain findings should prompt a referral for a full echocardiogram. Nephrologists with advanced echocardiography training can take FoCUS further, assessing stroke volume, estimating pulmonary artery pressure, and evaluating diastolic dysfunction, all of which can aid in managing complex cases.

VEXUS

Increased cardiac filling pressures are a key pathophysiologic change in heart failure. The backward transmission of this pressure to the systemic and pulmonary venous systems leads to classic signs and symptoms of congestion. When elevated central venous pressure (CVP) extends to abdominal organs and impedes venous outflow, it can cause dysfunction, such as liver and kidney injury. The term 'congestive nephropathy' has been suggested to describe this mechanism, which combines increased filling pressures, reduced venous compliance, and renal interstitial edema—leading to a condition akin to tamponade within the encapsulated kidney[50,51]. VExUS has emerged as a tool to assess venous congestion in the abdominal compartment, particularly relevant in right-sided heart failure. It involves measuring IVC diameter and collapsibility, as well as evaluating Doppler waveforms of the hepatic, portal, and renal parenchymal veins.

IVC diameter and respiratory variation are widely used as surrogate markers for CVP. Current guidelines state that an IVC diameter greater than 2.1 cm with less than 50% collapsibility during inspiration indicates elevated right atrial pressure between 10 and 20 mmHg[52]. However, it is crucial to note that IVC dilation can occur due to conditions unrelated to hypervolemia, such as severe tricuspid regurgitation, pulmonary hypertension, pneumothorax, pulmonary embolism, cardiac tamponade, or even in physiologic states like in young athletes. Therefore, using IVC ultrasound alone, without incorporating FoCUS and LUS, is strongly discouraged, as it may lead to inappropriate clinical decisions. Evaluating the IVC is the initial step in assessing venous congestion, as elevated CVP is a key determinant of this condition. Visualizing the IVC in both long and short axis planes can help minimize measurement errors[53-55]. VExUS involves Doppler evaluation of the hepatic, portal, and intrarenal veins to quantify venous congestion as described in Figure 4. Since these waveforms are dynamic, VExUS enables monitoring the effectiveness of decongestive therapy. This is valuable for nephrologists who must make decisions about fluid removal in non-ICU and clinic patients where invasive hemodynamic monitoring is not available. Figure 5 illustrates a case where these waveforms showed improvement with treatment visually guiding the clinician. On the other hand, each Doppler parameter has its limitations. For example, hepatic vein flow may be abnormal at baseline in severe tricuspid regurgitation; the absence of a simultaneous electrocardiogram can lead to significant interpretive errors; portal vein flow may appear more pulsatile in chronic liver disease; and renal venous flow can be abnormal in advanced CKD and technically challenging to assess due to patient breathing [56]. Thus, it is crucial to perform a multiorgan POCUS and integrate all clinical and biochemical information.

OVERCOMING BARRIERS TO POCUS ADOPTION: CHALLENGES, MISCONCEPTIONS, AND THE PATH FORWARD

Performing POCUS requires access to ultrasound equipment, but this has become less of a hurdle due to the increasing availability of portable and ultra-portable devices, as well as the potential to bill for the studies depending on institutional

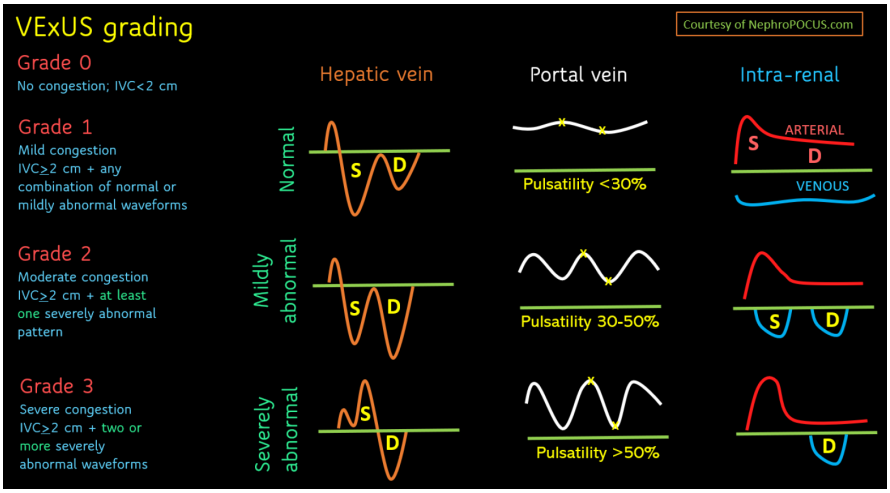

Figure 4 Venous excess ultrasound grading score. When inferior vena cava has a diameter > 2 cm, hepatic, portal, and rein vein waveforms should be checked. The abnormalities present in these venous Doppler waveforms correlate with the severity of congestion. Hepatic vein Doppler is considered mildly abnormal when the S wave is smaller than the D wave, but still below the baseline; it is considered severely abnormal when the S wave is reversed. Portal vein Doppler is considered mildly abnormal when the pulsatility is 30%-50%, and severely abnormal when it is ≥ 50%. Intrarenal vein Doppler is mildly abnormal when it is pulsatile with distinct S and D components, and severely abnormal when it is monophasic with a D-only pattern. This figure was adapted from NephroPOCUS.com with permission. The corresponding author Koratala A is the owner of the website and copyright holder[60]. See: https://nephropocus.com/about/.

infrastructure and local regulations. However, the challenge of providing adequate training for nephrologists to perform and interpret POCUS findings remains significant. Currently, the number of nephrologists trained in multi-organ POCUS is very limited, often necessitating reliance on workshops and courses to build skills in image acquisition and interpretation. While these educational opportunities are valuable for beginners, offering real-time feedback, they have limitations, including being resource-intensive and challenging to scale for larger groups. Books, blogs, and social media can also aid in learning and dissemination but lack the hands-on training necessary for proficiency[57]. Inadequate skills and reliance on isolated sonographic parameters, such as IVC or LUS, without comprehensive clinical context, can lead to potential patient harm (Figure 6).

As medical schools increasingly integrate POCUS into their curricula, more nephrology organizations are advocating for continuous POCUS training during fellowship and objective competency assessment[24,57]. Another barrier to adoption can be the concern about conflicts with radiologists or cardiologists, who may perceive nephrologists as encroaching on their expertise. However, the goal of POCUS is to provide a bedside, clinically oriented examination to address specific questions and guide management, while comprehensive evaluations by radiologists or cardiologists involve a detailed assessment of anatomical regions with predefined parameters and measurements. It is important to engage with these specialists at the institutional level to resolve issues and streamline processes. Additionally, these experts can serve as a quality check until a sufficient number of nephrologists proficient in POCUS are available at each institution. Without proper quality improvements and competency assessments, POCUS risks failing to deliver its full benefits to nephrologists.

Much of the skepticism about POCUS stems from a lack of robust evidence showing that it directly improves hard outcomes like mortality. We believe this perspective is flawed: A diagnostic tool alone cannot alter outcomes unless it is followed by effective treatment, just as a kidney biopsy alone does not improve outcomes in glomerulonephritis without subsequent treatment. POCUS enhances clinical practice by enabling real-time interpretation of pathophysiology at the bedside, allowing for more personalized treatment rather than applying a generic approach. In the modern era, dismissing a tool that improves diagnostic accuracy, accelerates care delivery, and enhances patient satisfaction based on its inability to directly improve mortality is not acceptable. Future research should explore the most effective applications of POCUS in nephrology-specific clinical scenarios and develop optimal management strategies based on its findings. Emphasis should be placed on practical outcomes, such as reducing time to accurate diagnosis, minimizing empiric therapies, decreasing recurrent hospitalizations, and enhancing patient understanding of their condition, rather than solely measuring its impact on mortality.

CONCLUSION

POCUS represents a significant advancement toward personalized medicine, and nephrologists should recognize the limitations of traditional physical examination and integrate POCUS into their practice. Its effectiveness relies not only on the operator's ability to acquire images but also on their broader clinical expertise, as with any medical tool. To maximize its potential, POCUS should be backed by structured, ongoing training and clearly defined competency standards.

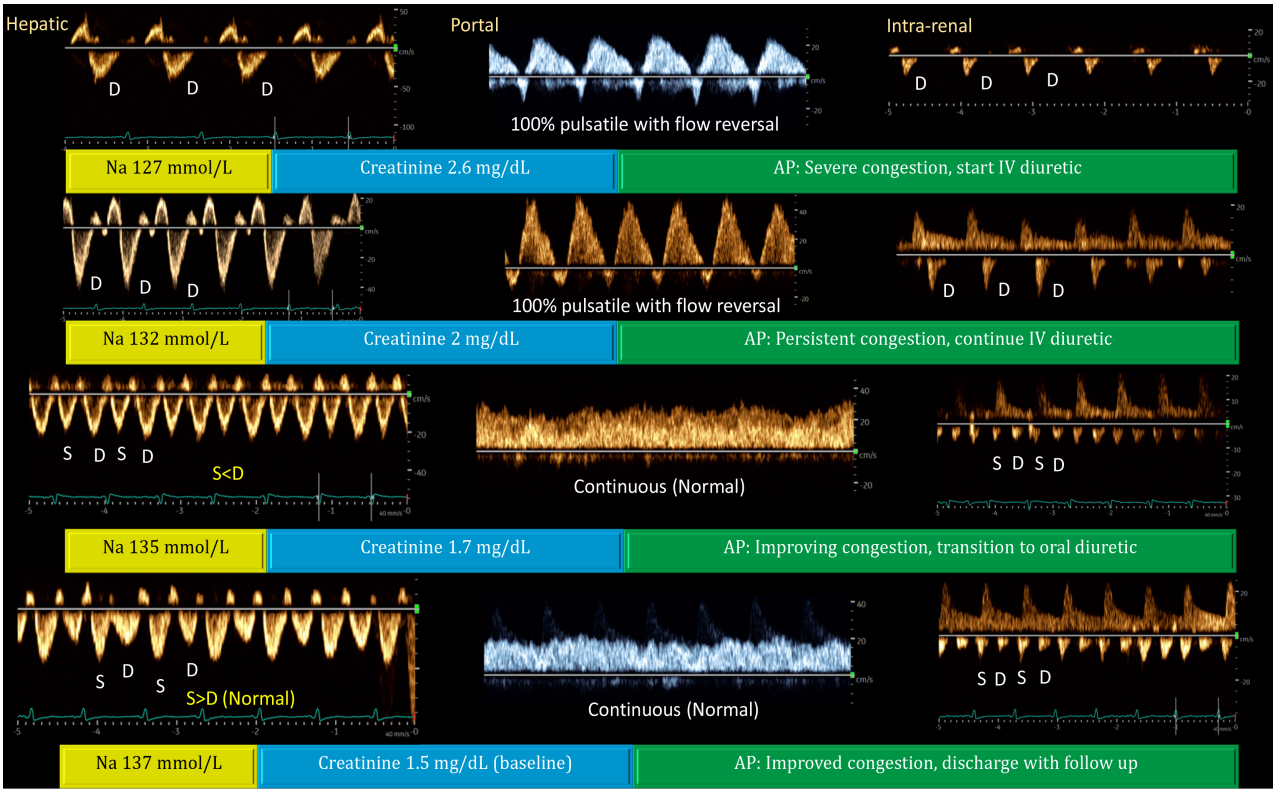

Figure 5 Doppler venous waveforms showing improvement (from top to bottom) in a patient with acute kidney injury and hyponatremia. In a physiological state, the hepatic vein Doppler resembles the central venous waveform, with a larger S-wave compared to the D-wave. As right atrial pressure (RAP) increases, the S-wave amplitude decreases and eventually reverses, leaving only the D-wave below the baseline. Normally, the portal vein flow is continuous (less than 30% pulsatility), but pulsatility increases with rising RAP, eventually leading to late-systolic flow reversal (below-baseline flow). Increased portal vein pulsatility may indicate gut congestion, potentially affecting diuretic absorption. The renal parenchymal vein, typically continuous (like the portal vein but below the baseline), becomes more pulsatile with increasing RAP, eventually showing distinct S- and D-waves with S-reversal similar to the hepatic vein. Generally, improvements in the portal vein precede those in the hepatic and renal veins, as shown above. Renal interstitial edema may delay recovery of the venous waveform. Reproduced from Koratala *et al*[61]. AP: Assessment and plan; S-wave: Systolic wave; D-wave: Diastolic wave. Citation: Koratala A, Ronco C, Kazory A. Multi-Organ Point-Of-Care Ultrasound in Acute Kidney Injury. *Blood Purif* 2022; 51: 967-971. Copyright © 2022 S. Karger AG. Published by Karger Publishers. The authors have obtained the permission for figure using (Supplementary material).

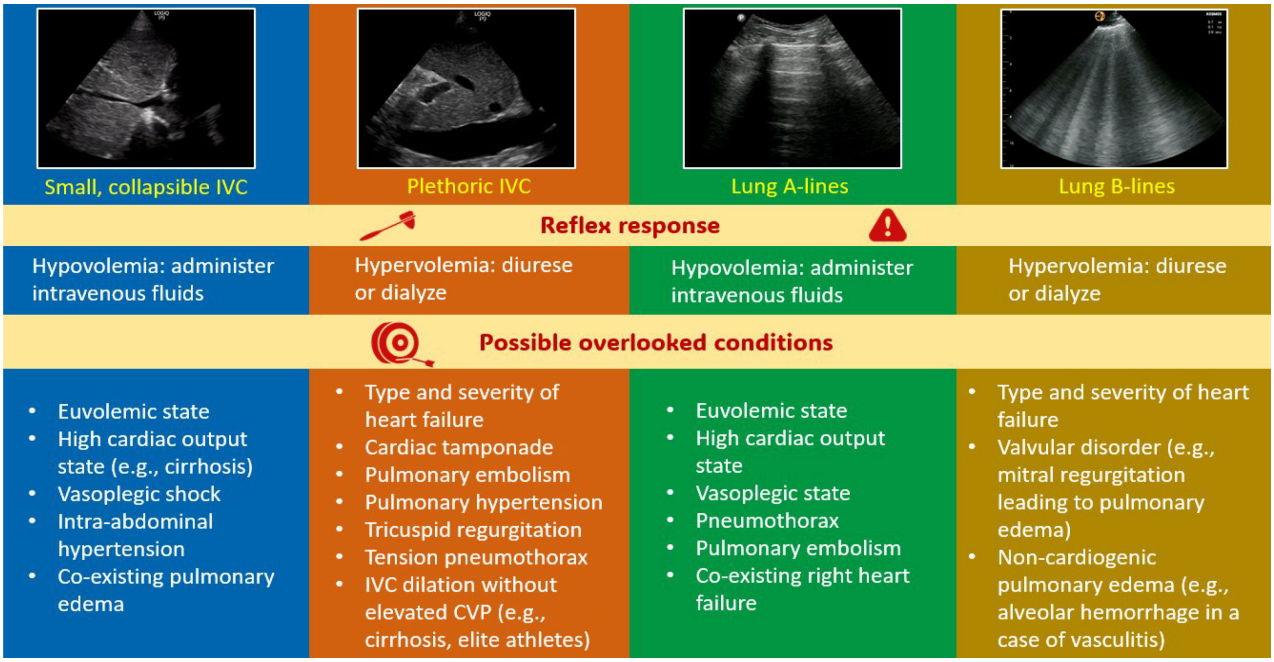

Figure 6 Pitfalls of excessive reliance on individual organ ultrasound and knee-jerk clinical decision-making. Comprehensive bedside

hemodynamic evaluation should almost always involve focused cardiac ultrasound, interpreting all these observations in the relevant clinical context. This applies to both initial diagnosis and monitoring selected parameters during follow-up examinations. *In intra-abdominal hypertension, inferior vena cava is small irrespective of central venous pressure and typically does not exhibit respiratory variation. Reproduced from Kazory *et al*[62]. IVC: Inferior vena cava; CVP: Central venous pressure. Citation: Kazory A, Olaoye OA, Koratala A. Nuances of Point-of-Care Ultrasound in Nephrology: A Clarion Call for Deeper Understanding. *Blood Purif* 2024; 53: 598-602.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Association between private insurance and living donor kidney transplant: Affordable Care Act as a natural experiment

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Abstract

BACKGROUND

Private insurance coverage is associated with higher rates of living donor kidney transplantation (LDKT) but whether this is attributable to confounding is not known.

AIM

To study the association between increased access to private health insurance and LDKT.

METHODS

Retrospective cohort study using United States transplant registry data. We identified incident candidates aged 22-29 years who were waitlisted for a kidney-only transplant from 2005-2014, excluding prior transplant recipients and those with missing data. We calculated the hazard of LDKT after waitlisting for those with private insurance *vs* other insurance pre-Affordable Care Act (ACA) *vs* post-ACA, using death and delisting as competing events, for candidates affected by the policy change (age 22-25 years) *vs* those who were not (age 26-29 years).

RESULTS

A total of 13817 candidates were included, of whom 46% were age 22-25 years and 54% were age 26-29 years. Among candidates aged 22-25 years at listing, those

listed post-ACA were more likely to have private insurance compared to those listed pre-ACA (42% *vs* 35%), but there was no difference in private insurance coverage between eras among candidates aged 26-29 years at listing. In adjusted competing risk regression, privately insured patients age 22-25 years were less likely to receive a LDKT post-ACA compared to pre-ACA [hazard ratio (HR) = 0.88, 95%CI: 0.78-1.00], as were those aged 22-25 years old with other insurance types (HR = 0.80, 95%CI: 0.69-0.92). These associations were not seen among candidates age 26-29 years.

CONCLUSION
Candidates age 22-25 years were likelier to have private insurance post-ACA, without an increased rate in LDKT. Demonstrations of associations between insurance and LDKT are likely attributable to residual confounding.

Key Words: Kidney transplant; End-stage kidney disease; Health policy; Health insurance; Transplantation

Core Tip: In this retrospective cohort study using United States transplant registry data from 2005-2014, we found that although kidney transplant candidates age 22-25 years were more likely to have private insurance following the Affordable Care Act policy change expanding eligibility to remain on parental insurance, this shift in payer mix was not associated with higher rates of living donor kidney transplantation. These data suggest that insurance type itself is not a direct determinant of access to living donor kidney transplant; rather the association of private insurance with higher transplantation rates in prior observational studies is likely a result of unmeasured demographic confounding.

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INTRODUCTION

Living donor kidney transplant is the optimal long-term treatment for patients with end-stage kidney disease (ESKD) given that it is a cost-effective solution[1,2] that has better long-term quality of life[3-6] and survival[7-10] outcomes over dialysis or deceased donor transplantation. Despite these benefits, only a minority of patients with ESKD in the United States ever receive a living donor transplant[11,12]. Several modifiable and unmodifiable socioeconomic and demographic factors are associated with disparities in access to kidney transplant, including race and ethnicity, older age, lower income, public insurance, and low educational attainment[11-14]. Across multiple studies, insurance type has been found to influence kidney transplant access, with patients with private insurance more likely than those with public insurance to be waitlisted, receive a transplant, or receive a living donor transplant specifically[11,13-15]. However, while these findings suggest that expansion of private coverage may be associated with improved transplant access, it is unclear if the observed disparities are due to benefits of private insurance directly, or rather confounded by other correlated socioeconomic advantages common among the privately insured population.

Following the implementation of the Affordable Care Act (ACA) in 2009, individuals who would normally have lost access to their parents' private insurance at age 22 years were permitted to remain on their parents' private plans until they reach age of 26 years. This change created a natural experiment enabling the study of the impact of private insurance coverage on living donor kidney transplantation (LDKT). Overall, the national volume of LDKT involving recipients of all ages remained similar before and after the policy change. Understanding changes in payer mix and the associated changes in preemptive waitlisting rates for patients with ESKD in the age group affected *vs* unaffected by this policy change *vs* others may elucidate the expected impact of increased access to private insurance and inform ESKD coverage policy initiatives. We hypothesized that, compared to young transplant candidates age 26-29 years not impacted by the policy change, those age 22-25 years at listing would have a greater proportion of private insurance coverage at the time of listing following ACA implantation but that rates of LDKT would be similar before and after the policy.

MATERIALS AND METHODS

We conducted a retrospective cohort study using United States transplant registry data from the Organ Procurement and Transplantation Network (OPTN) Standard Transplant Analysis and Research data set. This study was approved by the institutional review board of Columbia University Medical Center. The analysis was done using deidentified data from a national registry of waitlisted patients, therefore informed consent was not required.

We identified all incident candidates aged 22 years to 29 years who were waitlisted for a kidney-only transplant from 2005 to 2014 (Supplementary Figure 1). This age range was selected to provide one group of candidates with expanded access to parental private insurance resulting from the ACA policy change (age 22-25 years), as well as a control group similar in age that did not have access to parental insurance before or after the policy change (age 26-29 years). This time period was used to reflect the time period following the ACA policy change to the rollout of the Kidney Allocation System, which was implemented in December 2014 and a period of equal duration before the policy change. We excluded patients who had received any prior solid organ transplant (n = 1793), or who had missing body mass index (BMI) and height or weight data (n = 182).

We classified the final cohort of candidates into four analytic groups based on age at listing and era: (1) 22-25 years olds waitlisted in 2005-2009 (pre-ACA); (2) 2010-2014 (post-ACA); (3) 26-29 years olds waitlisted in 2005-2009 (pre-ACA); and (4) 2010-2014 (post-ACA). Follow up time was truncated six years after waitlisting date.

Statistical analysis

Candidate characteristics at the time of waitlisting were compared between the two eras within age groups using Pearson χ^2 tests for categorical variables, and Kruskal-Wallis tests for continuous variables. Column percentages are given for categorical characteristics. Medians with interquartile ranges are presented for continuous characteristics. Candidate characteristics were then also compared between patients with private insurance *vs* other insurance types among patients aged 22-25 years old in each era.

We used competing risks regression to assess the likelihood of LDKT after waitlisting in the presence of competing risks by calculating the cumulative incidence function for the probability of LDKT and treating deceased donor kidney transplantation, death, and waitlist removal as competing events. We first used unadjusted competing risk regression to determine the subhazard of LDKT by era, separately for each age group (*i.e.* 22-25 years and 26-29 years). We next computed adjusted regression models including age at listing, sex, race, BMI at listing, diabetes status, educational attainment, employment status, cause of kidney disease, preemptive listing status, and insurance type. We then repeated these competing risk regression models after further stratifying each age group by insurance type (private *vs* all others).

Sensitivity analysis

In order to determine if the observed effect was due primarily to an increase of patients on Medicaid, whose expansion was also part of the ACA, we conducted a sensitivity analysis repeating the same competing risk analysis, unadjusted and adjusted, limited to candidates residing in the twenty-four states that did not expand Medicaid prior to January 1, 2015 (Alabama, Alaska, Florida, Georgia, Idaho, Indiana, Kansas, Louisiana, Maine, Mississippi, Missouri, Montana, Nebraska, North Carolina, Oklahoma, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Wisconsin, and Wyoming).

RESULTS

A total of 13817 kidney transplant candidates with age 22-29 years who were added to the waitlist from 2005-2014 were included in the analysis, of whom 6308 (46%) were age 22-25 years and 7509 (54%) were age 26-29 years (Supplementary Figure 1) at listing. Both age groups were similar, with White race and male sex being the largest categories in both (Table 1). When comparing candidate characteristics in each age group before ACA implementation (2005-2009) and after ACA implementation (2010-2014), sex, race, employment status, and pre-listing dialysis use were similar between eras for both groups.

Among candidates aged 22-25 years at listing, those listed between 2010-2014 (post-ACA) were significantly more likely to have private insurance compared to those listed from 2005-2009 (pre-ACA) (42% *vs* 35%) (Table 1). However, there was no significant difference in private insurance coverage between eras observed in the 26-29 years age group not impacted by the ACA policy change (39% in both eras).

When examining candidates age 22-25 years at listing, the demographics of those who had private insurance were similar among those listed 2005-2009 *vs* 2010-2014 (Supplementary Table 1). Privately insured candidates were most commonly of White race and male sex. Privately insured candidates also most commonly had a high school diploma or general equivalency diploma, glomerulonephritis as primary disease, and were not pre-emptively waitlisted before initiating dialysis. Although there was an observed increase in the proportion of patients who were listed as not employed (2005-2009: 39%, 2010-2014: 46%), this was paired with a similar decrease in employment status listed as "missing/unknown".

Despite the difference in payor mix between eras for the age 22-25 years group, there was no significant difference in the observed proportion receiving a living donor transplant by end of follow up (Table 1). Similarly, there was no difference between eras in the proportion of candidates aged 26-29 years at listing who received a living donor transplant. Among all groups, the cumulative incidence of living donor kidney transplant was highest for candidates aged 22-25 years pre-ACA, followed by 22-25 years post-ACA, then 26-29 years post-ACA, and finally 26-29 years pre-ACA (Figure 1A). This order was similar when limiting the analysis only to candidates with private insurance or only candidates with other insurance types (Figure 1B and C).

In adjusted competing risk regression, privately insured patients ages 22-25 years were less likely to receive a living donor kidney transplant post-ACA compared to pre-ACA [hazard ratio (HR) = 0.88, 95% CI: 0.78-1.00, P = 0.04], as were patients aged 22-25 years old with other types of insurance (HR = 0.80, 95% CI: 0.69-0.92, P = 0.002) (Table 2). These associations were not seen among candidates aged 26-29 years at listing (Table 2).

Table 1 Characteristics of kidney transplant candidates included in the analytic cohort, *n* (%)

	22-25 years old				26-29 years old			
	All	2005-2009 (pre-ACA)	2010-2014 (post-ACA)	*P* value	All	2005-2009 (pre-ACA)	2010-2014 (post-ACA)	*P* value
Age at listing (year) (median, 25%th-75%th)	24 (23, 25)	24 (23, 25)	24 (23, 25)	0.0062	28 (27, 29)	28 (27, 29)	28 (27, 29)	0.1773
Race/ethnicity								
White	2543 (38.84)	1250 (38.83)	1293 (38.85)	0.205	2993 (36.96)	1516 (37.08)	1477 (36.843	0.367
Black	1871 (28.58)	949 (29.48)	922 (27.70)		2559 (31.60)	1316 (32.18)	1243 (31.00)	
Hispanic	1606 (24.53)	779 (24.20)	827 (24.85)		1785 (22.04)	892 (21.81)	893 (22.27)	
Other	527 (8.05)	241 (7.49)	286 (8.59)		762 (9.41)	365 (8.93)	397 (9.90)	
Gender								
Male	3692 (56.39)	1803 (56.01)	1889 (56.76)	0.558	4376 (54.03)	2182 (53.36)	2194 (54.71)	0.219
Female	2855 (43.61)	1415 (43.99)	1439 (43.24)		3723 (45.97)	1907 (46.64)	1816 (45.29)	
Body mass index (kg/m^2)	24.33 (21.27, 29.15)	24.41 (21.33, 29.03)	24.23 (21.16, 29.23)	0.431	25.59 (22.15, 30.29)	25.46 (22.13, 30.00)	25.72 (22.19, 30.78)	0.0088
Diabetes status								
No diabetes	6120 (93.48)	2994 (93.01)	3126 (93.93)		6789 (83.39)	3410 (83.39)	3379 (84.26)	
Diabetes	427 (6.52)	225 (6.99)	202 (6.07)	0.132	1310 (16.17)	679 (16.61)	631 (15.74)	0.288
Educational attainment								
Less than high school	249 (3.80)	136 (4.22)	113 (3.40)	< 0.001	330 (4.07)	171 (4.18)	159 (3.97)	< 0.001
High school graduate or general equivalency diploma	3136 (47.89)	1572 (48.84)	1564 (47.00)		3549 (43.71)	1784 (43.63)	1756 (43.79)	
Some college	2060 (31.46)	901 (27.99)	1159 (34.83)		2234 (27.58)	1049 (25.65)	1185 (29.55)	
College graduate or higher	771 (11.78)	342 (10.62)	429 (12.89)		1498 (18.50)	689 (16.85)	809 (20.17)	
Missing or unknown	331 (5.06)	269 (8.33)	63 (1.89)		497 (6.14)	396 (9.68)	101 (2.52)	
Employment status								
Not employed	4200 (64.15)	1998 (62.07)	2202 (66.17)	< 0.001	4776 (58.97)	2345 (57.35)	2431 (60.62)	< 0.001
Employed	2004 (30.61)	980 (30.44)	1024 (30.77)		2891 (35.70)	1419 (34.70)	1472 (36.71)	
Missing or unknown	343 (5.24)	241 (7.49)	102 (3.06)		432 (5.33)	325 (7.95)	107 (2.67)	
Primary cause of renal failure								
Cystic kidney disease	137 (2.09)	55 (1.71)	82 (2.46)	0.019	197 (2.43)	82 (2.01)	115 (2.87)	0.001
Diabetes mellitus	298 (4.55)	164 (5.09)	134 (4.03)		1110 (13.71)	565 (13.82)	545 (13.59)	
Hypertension	1017 (15.53)	525 (16.31)	492 (14.78)		1461 (18.04)	775 (18.95)	686 (17.11)	
Glomerulonephritis	2837 (43.33)	1375 (42.72)	1462 (43.93)		3231 (39.89)	1567 (38.32)	1664 (41.50)	
Other/unknown	2258 (34.49)	1100 (34.17)	1158 (34.80)		2100 (25.93)	1100 (26.90)	1000 (24.94)	
Pre-emptively waitlisted								
No	5155 (28.74)	2588 (80.40)	2567 (77.13)	0.001	6170 (76.18)	3190 (78.01)	2980 (74.31)	< 0.001
Yes	1392 (21.26)	631 (19.60)	761 (22.87)		1929 (23.82)	899 (21.99)	1030 (25.69)	
Primary payer at waitlist registration								
Private	2537 (38.75)	1140 (35.41)	1397 (41.98)	< 0.001	3156 (38.97)	1602 (39.18)	1554 (38.75)	0.090
Medicare	2634 (40.23)	1371 (42.59)	1263 (37.95)		3397 (41.94)	1736 (42.46)	1661 (41.42)	
Medicaid	1184 (18.08)	599 (18.61)	585 (17.58)		1322 (16.32)	629 (15.38)	693 (17.28)	
All others	192 (2.93)	109 (3.39)	83 (2.49)		224 (2.77)	122 (2.98)	102 (2.54)	

Waitlist outcomes								
Deceased donor transplant	2416 (36.90)	1191 (37.00)	1225 (36.81)	< 0.001	2988 (36.89)	1563 (38.22)	1425 (35.54)	< 0.001
Living donor transplant	1858 (28.38)	933 (28.98)	925 (27.79)		2036 (25.14)	1014 (24.80)	1022 (25.49)	
Died on waitlist	427 (6.52)	251 (7.80)	176 (5.29)		591 (7.30)	357 (8.73)	234 (5.84)	
Removed from waitlist for reason other than transplant or death	1648 (25.17)	804 (24.98)	844 (25.36)		2258 (27.88)	1114 (27.24)	1144 (28.53)	
Still on waitlist	198 (3.02)	40 (1.24)	158 (4.75)		226 (2.79)	41 (1.00)	185 (4.61)	

ACA: Affordable Care Act.

Table 2 Competing risk model for living donor kidney transplants

	Unadjusted			Adjusted model[1]		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age 22-25 years (Group Impacted By Policy Change)						
Post-ACA *vs* pre-ACA, whole cohort	0.95	0.87-1.04	0.26	0.85	0.77-0.93	0.001
Post-ACA *vs* pre-ACA, privately insured	0.92	0.81-1.03	0.15	0.88	0.78-1.00	0.04
Post-ACA *vs* pre-ACA, no private insurance	0.84	0.73-0.97	0.02	0.80	0.69-0.92	0.002
Age 26-30 years (Control Group)						
Post-ACA *vs* pre-ACA, whole cohort	1.03	0.94-1.13	0.48	1.00	0.91-1.09	0.98
Post-ACA *vs* pre-ACA, privately insured	1.07	0.95-1.19	0.28	1.01	0.90-1.14	0.82
Post-ACA *vs* pre-ACA, no private insurance	1.01	0.88-1.16	0.92	0.98	0.85-1.13	0.77

[1]Adjusted model includes age at listing, sex, race, body mass index as listing, diabetes status, educational attainment, employment status, cause of kidney disease, preemptive listing status, and (in whole cohort models only) insurance type.
ACA: Affordable Care Act; HR: Hazard ratio.

Results were similar in a sensitivity analysis restricted to candidates listed in states without Medicaid expansion (Supplementary Table 2).

DISCUSSION

In this retrospective cohort study using United States transplant registry data from 2005-2014, we found that although kidney transplant candidates age 22-25 years were more likely to have private insurance following the ACA policy change expanding eligibility to remain on parental insurance, this shift in payer mix was not associated with a higher rate of LDKT. Rather, both privately insured candidates and candidates with other forms of insurance in this age group appear to be less likely to receive a living donor kidney transplant after the ACA, an effect that was not observed in the older cohort not affected by the ACA policy change. These data suggest that, in this young adult population, insurance type itself is not a direct determinant of access to living donor kidney transplant; rather the association of private insurance with higher transplantation rates in prior observational studies is likely a result of unmeasured demographic confounding—*i.e.* characteristics of the privately insured population.

The association of private insurance coverage and outcomes for patients with ESKD has been of increased interest following the Marietta Memorial Hospital Employee Health Benefit Plan v. DaVita Inc. decision by the Supreme Court in June 2022[16]. As a result of that decision, it is possible that in coming years, it will be more difficult for patients with ESKD to maintain their private insurance, making it essential to understand the potential implications of this on access to transplantation–and in particular living donor transplantation. However, given the many dissimilarities between individuals with access to different types of insurance, it is difficult to say whether insurance type itself affects patient outcomes instead of an unmeasured confounding factor. By using a natural experiment design with a built in intervention and control group, with the implementation of the ACA as the intervention, we can better study whether or not gaining access to private insurance itself leads to increased rates of living donor transplantation.

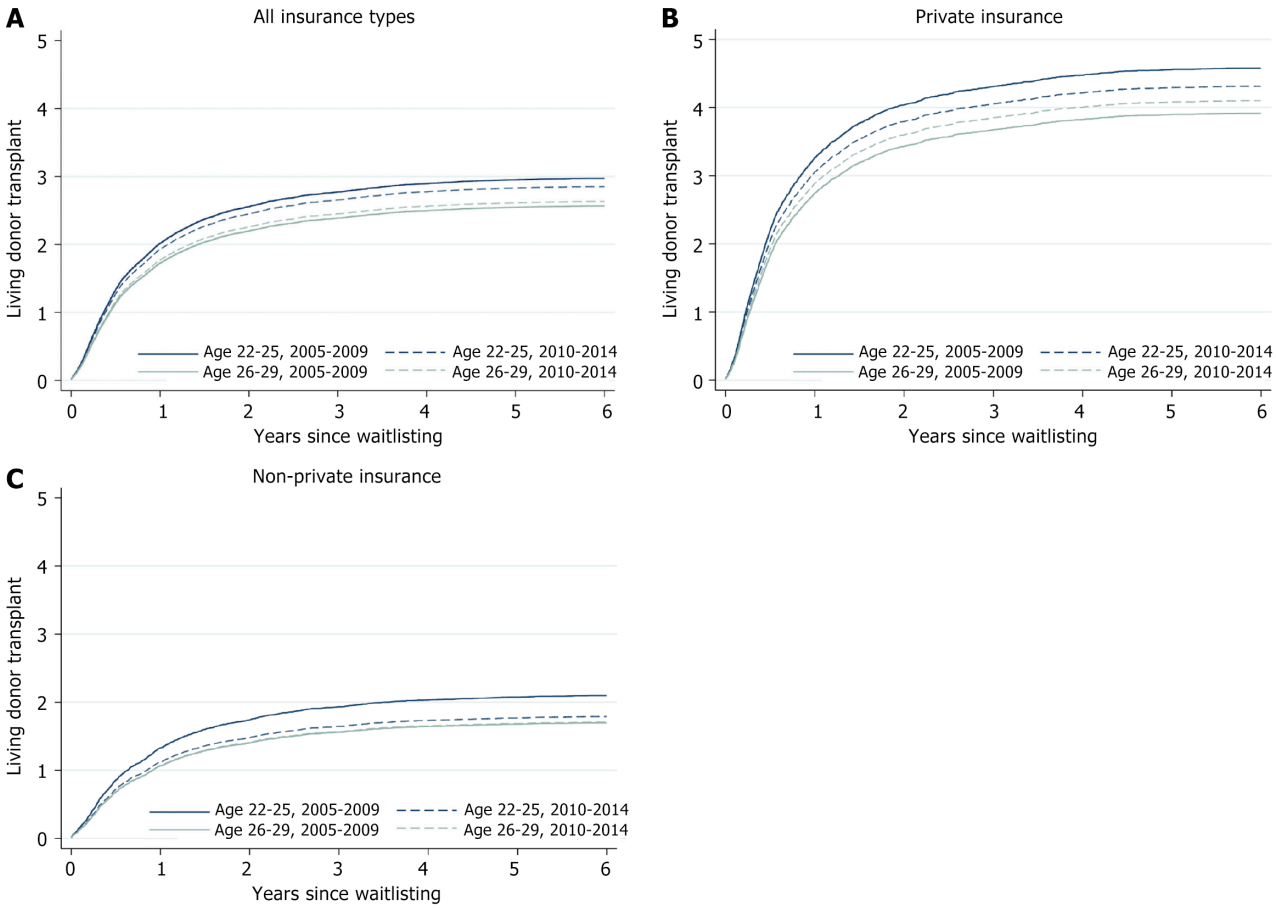

Figure 1 The calculated unadjusted cumulative incidence of living donor kidney transplant among candidates. A: All insurance types; B: Private insurance; C: Non-private insurance.

Previous literature suggested that patients with private insurance are more likely to be evaluated, waitlisted, receive any transplant, and receive a living donor transplant compared to patients with public insurance (*i.e.* Medicare or Medicaid), so it would follow that expansion of private insurance in any group would improve health outcomes in that group[13-15]. Our findings to the contrary suggest that interventions aimed at expanding access to specific types of insurance are unlikely to impact living donor transplant rates. They also emphasize the need for better capture of individual-level socioeconomic status data in national transplant registries in order to better understand and address disparities in access to transplantation. More importantly, however, they suggest that expansion of public coverage to medically vulnerable populations is not likely to provide inferior outcomes compared to private insurance coverage.

Paradoxically, we found that even though private insurance was associated with a higher rate of living donor transplantation than other types of insurance, despite a post-ACA shift towards more private insurance coverage among candidates age 22-25 years, these candidates were less likely to receive a living donor transplant post-ACA, an effect that was also observed when analyzing only candidates with private insurance or only those with other forms of insurance. We hypothesize that understanding insurance type as capturing one dimension of a multi-dimensional concept of socioeconomic status helps reconcile these findings (Figure 2). Candidates can be conceptually divided into three groups with decreased socioeconomic advantage: (1) An employed group with independent access to private insurance; (2) A group with no independent private insurance access but parents who are privately insured; and (3) A group with no independent private insurance for either the patients or the parents. The second group would have been part of the "non-privately insured group" prior to the ACA and then part of the "privately insured group" after the ACA. As a result, the socioeconomic status of both privately insured candidates and other candidates age 22-25 years decreased post-ACA, as the most advantaged candidates among those who previously would have been non-privately insured were instead privately insured.

Strengths of our study included the use of the ACA as a "natural experiment" to assess the association between insurance and health outcomes for patients with ESKD in the absence of an ability to conduct a clinical trial. Limitations include the inability to account for other key individual-level socioeconomic characteristics that are not included in the OPTN registry, including income data. Further, in the absence of randomized trial data assigning candidates to different insurance types, the lack of an association between insurance type and living donor transplantation that we observed is itself possibly subject to residual confounding. However, we believe that other investigators may consider using a similar natural experiment design around the ACA's implementation to study the association between payer type and outcomes in other health domains.

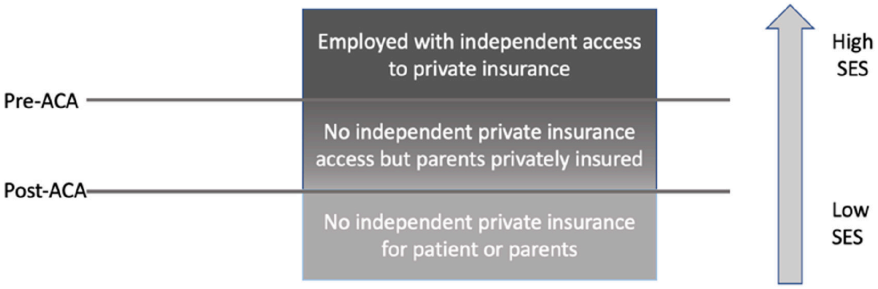

Figure 2 Conceptual diagram of proposed mechanism of study findings. We hypothesize that the fall in living donor kidney transplantation rates among candidates with either private insurance or other insurance types is attributable to confounding by socioeconomic status, whereby candidates with intermediate socioeconomic status (*i.e.* those with access to parental private insurance) moved from public insurance to private insurance, thus lowering the group-level socioeconomic status of both privately insured candidates and non-privately insured candidates. ACA: Affordable Care Act; SES: Socioeconomic status.

CONCLUSION

In conclusion, we found that although kidney transplant candidates age 22-25 years were more likely to have private insurance post-ACA compared to pre-ACA, those listed in the post-ACA period were less likely to receive a living donor transplant. This result suggests that insurance type itself is not independently associated with living donor transplant rates, but instead that prior demonstrations of associations between insurance and living donor transplantation were likely attributable to residual confounding. Further research is needed to elucidate how to develop insurance expansion strategies that optimize transplant rates.

FOOTNOTES

Author contributions: Perry K was responsible for data curation; Perry K and Husain SA were responsible for methodology, formal analysis and writing original draft; Adler JT, Mohan S, and Husain SA were responsible for supervision; Mohan S and Husain SA were responsible for resources; Husain SA was responsible for funding acquisition; Perry K, Yu M, Adler JT, Maclay LM, Cron DC, Mohan S, and Husain SA were responsible for conceptualization, investigation, writing review and editing, and visualization; all of the authors read and approved the final version of the manuscript to be published.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Investigating the controversial link between pediatric obesity and graft survival in kidney transplantation

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Abstract

BACKGROUND

Childhood obesity is a significant public health concern, particularly amongst children with chronic kidney disease requiring kidney transplant (KT). Obesity, defined as a body mass index (BMI) of 30 kg/m² or greater, is prevalent in this population and is associated with disease progression. While BMI in-fluences adult KT eligibility, its impact on pediatric transplant outcomes remains unclear. This study investigates the effect of BMI on graft survival and patient outcomes, addressing gaps in the literature and examining disparities across BMI classifications.

AIM

To assess the impact of BMI classifications on graft and patient survival following KT.

METHODS

A retrospective cohort study analyzed 23081 pediatric transplant recipients from the Standard Transplant Analysis and Research database (1987-2022). Patients were grouped into six BMI categories: Underweight, healthy weight, overweight, and Class 1, 2, and 3 obesity. Data were analyzed using one-way way analysis of variance, Kruskal-Wallis tests, Chi-squared tests, Kaplan-Meier survival analysis with log-rank tests, and Cox proportional hazard regressions. Statistical significance was set at $P < 0.05$.

RESULTS

Class 3 obese recipients had lower 1-year graft survival (88.7%) compared to healthy-weight recipients (93.1%, $P = 0.012$). Underweight recipients had lower 10-year patient survival (81.3%, $P < 0.05$) than healthy-weight recipients. Class 2

and 3 obese recipients had the lowest 5-year graft survival (67.8% and 68.3%, $P = 0.013$) and Class 2 obesity had the lowest 10-year graft survival (40.7%). Cox regression identified increases in BMI category as an independent predictor of graft failure [hazard ratio (HR) = 1.091, $P < 0.001$] and mortality (HR = 1.079, $P = 0.008$). Obese patients experienced longer cold ischemia times (11.6 and 13.1 hours *vs* 10.2 hours, $P < 0.001$). Class 3 obesity had the highest proportion of Black recipients (26.2% *vs* 17.9%, $P < 0.001$).

CONCLUSION
Severe obesity and underweight status are associated with poorer long-term outcomes in pediatric KT recipients, emphasizing the need for nuanced transplant eligibility criteria addressing obesity-related risks and socioeconomic disparities.

Key Words: Kidney; Transplantation; Graft failure; Pediatric; Obesity; Underweight

Core Tip: This study investigates the relationship between pediatric obesity and kidney transplant outcomes, addressing a gap in research by analyzing graft survival across body mass index categories. While short-term outcomes for overweight and Class 1 obese pediatric recipients are comparable to healthy-weight peers, Class 2 and 3 obese patients experience significantly reduced long-term graft survival. Underweight recipients also exhibit poorer outcomes, highlighting the dual risks of obesity and malnutrition. The findings highlight the need for individualized transplant criteria and targeted interventions for severely obese children, emphasizing the role of socioeconomic and racial disparities in pediatric kidney transplantation.

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INTRODUCTION

The childhood obesity epidemic is a pressing public health issue with far-reaching implications, particularly in the context of medical interventions like kidney transplantation (KT). Obesity, defined as a body mass index (BMI) of 30 kg/m^2 or greater, is increasingly common among children with chronic kidney disease (CKD) and has been independently associated with both the progression of CKD and the eventual development of kidney failure[1]. In adults, obesity is a well-established risk factor for adverse KT outcomes, leading to complications including surgical site infections, extended hospital stays, delayed graft function (DGF), and, ultimately, reduced long-term graft and patient survival[2,3]. Both CKD and obesity are associated with systemic inflammation, and their cumulative impact may be the link contributing to poorer graft survival in obese patients. Elevated red cell distribution width, reflecting inflammation, is independently associated with higher mortality in CKD and transplant recipients[4]. Similarly, mean platelet volume, correlated with BMI and waist circumference, highlights the systemic impact of obesity-related inflammation[5]. Because of the well-documented risks of transplantation in obese patients, BMI has become a relative or even absolute contraindication in both pediatric and adult populations, depending on the transplant center. However, the evidence that underpins this policy is largely based on adult studies, with limited empirical data available to guide decisions in pediatric KT. The ethical considerations surrounding the use of BMI as a criterion for pediatric KT are significant and controversial. While some transplant centers recommend obese candidates to lose weight before surgery, the prolonged wait for weight loss can increase the risk associated with extended dialysis, which in itself poses life-threatening complications[6]. In adult obese dialysis patients, there is an "obesity paradox," in which there was a lower risk of death in patients with a BMI between 30-34.9[7]. One hypothesis for this is that obesity may protect against protein-energy wasting; others implicate the dangerous comorbidities associated with a low BMI[8,9]. Regardless of the mechanism, this phenomenon does not carry into the pediatric population, as obesity is associated with increased mortality compared to normal-weight children on dialysis[10]. Despite potential delays, previous literature suggests that weight loss, either achieved by lifestyle modifications or bariatric surgery, can improve transplant outcomes[9]. Additionally, the dynamics of childhood obesity, which are heavily influenced by socioeconomic, genetic, and environmental factors beyond the child's control, further complicate the fairness of using BMI as a strict determinant for eligibility. Pediatric obesity is often linked to systemic inequities, with high rates in Black and Hispanic households, particularly those with lower socioeconomic status[11]. Food insecurity is a durable predictor of the development of obesity, both in childhood and in adulthood[12]. It becomes critical to reassess transplant candidacy criteria that disproportionally affect vulnerable populations, which becomes especially important in pediatrics. Despite the known risks of obesity, little research has been done to evaluate how BMI affects pediatric KT outcomes, and the studies that exist have produced mixed results. This study aims to fill critical gaps in understanding the influence of BMI on pediatric KT outcomes by evaluating

survival metrics, including graft and patient survival, across BMI classifications. It further investigates disparities in transplant-related variables among BMI groups and examines the long-term impact of elevated BMI on transplant success. The findings aim to inform and enhance clinical decision-making. We hypothesize that higher BMI is inversely associated with graft and patient survival, with obese recipients experiencing poorer outcomes than their healthy-weight counterparts. Most importantly, we propose that socioeconomic and demographic disparities significantly contribute to outcome variations across BMI groups, specifically within the pediatric population, highlighting the need for equitable and comprehensive transplant criteria.

MATERIALS AND METHODS

Subjects and data collection

The Standard Transplant Analysis and Research (STAR) database was utilized to identify subjects and gather data. This database contains de-identified information on all donors, wait-list candidates, and transplant recipients in the United States. It is managed by the United States Department of Health and Human Services and the Health Resources and Services Administration and is maintained by the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network. Given the retrospective nature of the study and the use of de-identified data, it was classified as exempt from formal institutional review by the institutional review board.

Inclusion and exclusion criteria

The STAR/UNOS database was used to identify KT recipients from January 1st, 1987, to December 31st, 2022. Recipients above the age of 18 were excluded. The selection criteria allowed for 23081 pediatric KT recipients to be included, who were further divided into one of six American Academy of Pediatrics BMI Classifications based on growth percentiles for age and sex: Underweight (< 5th percentile); Healthy Weight (5th-85th percentile); Overweight (85th-95th percentile); Class 1 Obesity (95th–120% of the 95th percentile or BMI 35); Class 2 Obesity (BMI = 35 or 120%–140% of the 95th percentile or BMI = 40); Class 3 Obesity (> 140% of the 95th percentile or BMI = 40). This is outlined in Figure 1. Transplantation eras were selected based on precedents established by previous research to reflect advancements in transplantation practices, ensure a sufficient sample size for statistical analysis, and account for changes in recipient and donor demographics over time[13].

Descriptive and comparative analyses

Statistical analyses were performed using IBM SPSS Statistics Version 30. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. For continuous variables that conformed to normality, one-way analysis of variance was used to compare differences between groups. For data that did not meet the assumption of normality, the Kruskal-Wallis test was employed as a non-parametric alternative to compare continuous variables across groups. Categorical variables were analyzed using Chi-squared tests. Asymptotic two-tailed significance *P*-values were reported for continuous and categorical variables. Graft survival (all-cause survival) between groups was evaluated using Kaplan-Meier survival analysis, and survival curves were compared using the log-rank test. Statistical significance for all tests was determined at the $P < 0.05$ threshold.

Cox proportional hazards regression analysis

Multivariate Cox proportional hazards regression models were used to identify independent predictors of graft and patient survival. Recipient-specific variables included age, ethnicity (Black, White, Hispanic, or Other) BMI, gender, and pre-existing diabetes status. Donor and transplant-specific variables included the degree of HLA mismatch, cold ischemia time (CIT), and transplant era. Hazard ratios (HRs), and 95%CI were calculated for each covariate to quantify their associations with graft failure and patient mortality.

RESULTS

As outlined in Table 1, 62% of patients were within a healthy weight range at the time of transplantation. 13.6% were overweight, 11.1% Class 1 obese, 3.1% Class 2 obese, and 1% Class 3 obese. Figure 2 illustrates a steady rise in overweight and obese patients over time, with 2022 marking equal proportions of overweight and Class I obese patients (14.1%) and a 10-year high in Class II obesity (5%). Table 1 also summarizes recipient and donor characteristics by BMI. Overweight and obese patients of all classes were significantly less likely to have living donors compared to healthy-weight individuals ($P < 0.05$), with the lowest rates among Class 2 obese patients (34.4% *vs* 42.8% for healthy-weight, $P < 0.001$). CIT were significantly higher for Class 2 and 3 obese patients (11.6- and 13.1-hours *vs* 10.2 hours for healthy-weight, $P < 0.001$). Obese patients were more likely to be male (66.7% in Class 3, 61.8% in Class 2, 63.6% in Class 1, *vs* 57.5% in healthy weight, $P < 0.05$). Overweight and Obese patients were more likely to be younger, with a 12-year average age for healthy weight compared to 11, 9, 11, and 10 years for overweight, Class 1, 2, and 3 obesity, respectively. Non-White patients, mainly Black and Hispanic patients, were overrepresented in overweight and obese groups, with Class 3 obesity showing the highest proportion of Black patients (26.2% *vs* 17.9%, $P < 0.001$). No significant differences were found between BMI groups in donor distance from the transplant center, Kidney Donor Profile Index (KDPI), donor sex, or DGF rates. There were also no differences in 1-year graft or patient survival across BMI categories. However, significant differences were

Table 1 Recipient and donor characteristics of pediatric kidney transplants separated by body mass index class, *n* (%)

Characteristic	Underweight (< 5th)	Healthy weight (5th-85th)	Overweight (85th-95th)	Class 1 obese (95th-120%95th)	Class 2 obese (120%-140%95th)	Class 3 obese (> 140%95th)
Transplant variables						
Transplants	2040 (8.8)	14361 (62.2)	3142 (13.6)	2588 (11.2)	725 (3.1)	225 (1.0)
Living donor type	864 (42.4)[c,d,e,f]	6143 (42.8)[c,d,e,f]	1220 (38.8)[a,b,e]	1013 (39.1)[a,b,e]	249 (34.3)[a,b,c,d,f]	80 (35.6)[a,b,e]
Mean cold ischemia time (SE) (hours)	11.0 (0.25)[b,c,d]	10.2 (0.09)[a,e,f]	10.9 (0.19)[a,e,f]	10.5 (0.39)[a,e,f]	11.6 (0.82)[b,c,d]	13.1[b,c,d]
Mean distance from transplant center (SE) (nmi)	93.6 (6.0)	87.9 (2.2)	90.8 (4.5)	89.4 (4.7)	96.0 (19.0)	115.2
Mean HLA mismatches (SE)	3.53 (0.03)	3.61 (0.01)	3.70 (0.03)	3.73 (0.03)	3.78 (0.06)	3.65 (0.10)
DGF	186 (9.1)	1174 (8.2)	267 (8.5)	248 (9.6)	61 (8.4)	22 (9.8)
Transplant era						
1987-1999	851 (41.0)	4240 (29.5)	828 (26.4)	680 (26.0)	191 (26.3)	100 (44.4)
2000-2003	208 (10.2)	1577 (11.0)	402 (12.8)	309 (11.9)	101 (13.9)	35 (15.6)
2004-2007	201 (9.9)	1959 (13.6)	413 (13.1)	368 (14.2)	119 (16.4)	26 (11.6)
2008-2011	218 (10.7)	1883 (13.1)	422 (13.4)	345 (13.3)	86 (11.9)	19 (8.4)
2012-2015	194 (9.5)	1770 (12.3)	401 (12.8)	331 (12.8)	82 (11.3)	17 (7.6)
2016-2019	234 (11.5)	1813 (12.6)	413 (13.1)	333 (12.9)	80 (11.0)	16 (7.1)
2020-2022	134 (6.6)	1117 (7.8)	263 (8.4)	222 (8.6)	66 (9.1)	12 (5.3)
Donor variables						
Mean age (SE) years	29.5 (0.29)[b,c,d,e,f]	29.4 (0.10)[a,c,d,e,f]	28.8 (0.22)[a,b,e,f]	27.6 (0.23)[a,b,e,f]	28.6 (0.44)[a,b,c,d]	27.2 (0.84)[a,b,c,d]
Male natal sex	1164 (57.1)	8065 (56.2)	1760 (56.0)	1423 (55.0)	416 (57.4)	129 (57.3)
Race or ethnicity						
White	1310 (64.2)[b,c,c,d,f]	9634 (67.1)[a,c,d,e,f]	2082 (66.3)[a,b,e,f]	1728 (66.8)[a,b,e,f]	1310 (64.2)[a,b,c,d,f]	9634 (67.1)[a,b,c,d,e]
Black	259 (12.7)	1681 (11.7)	390 (12.4)	334 (12.9)	259 (12.7)	1681 (11.7)
Hispanic	379 (18.6)	2590 (18.0)	575 (18.3)	444 (17.2)	379 (18.6)	2590 (18.0)
Asian	62 (3.0)	276 (1.9)	63 (2.0%)	49 (1.9)	62 (3)	276 (1.9)
Multiracial/other	30 (1.4)	180 (1.2)	32 (1.0)	33 (1.3)	30 (1.4)	180 (1.2)
Mean donor BMI (SE)	24.9 (0.139)[e,f]	25.3 (0.050)[e,f]	25.4 (0.107)[e,f]	25.3 (0.121)[e,f]	26.1 (0.246)[a,b,c,d,f]	24.6 (0.462)[a,b,c,d,e]
Mean KDPI (SE)	177 (0.005)	0.167 (0.002)	0.170 (0.004)	0.171 (0.004)	0.168 (0.007)	0.172 (0.013)
Recipient variables						
Median age (75th-25th)	12.9 (0.09)[c,d,e,f]	11.9 (0.04)[c,d,e,f]	10.7 (0.09)[a,b]	9.23 (0.11)[a,b]	11.1 (0.19)[a,b]	10.3 (0.33)[a,b]
Male natal sex	1188 (58.2)[d,e,f]	8254 (57.5)[d,e,f]	1827 (58.1)[d,e,f]	1646 (63.6)[a,b,c]	448 (61.8)[a,b,c]	150 (66.7)[a,b,c]
Race or ethnicity						
White	1106 (54.2)[c,d,e,f]	7837 (54.6)[c,d,e,f]	1634 (52.0)[a,b,e]	1347 (52.0)[a,b,e]	356 (49.1)[a,b,c,d,f]	119 (52.9)[a,b,e]
Black	400 (19.6)	2566 (17.9)	598 (19.0)	479 (18.5)	149 (20.6)	59 (26.2)
Hispanic	394 (19.3)	3209 (22.3)	747 (23.8)	635 (24.5)	182 (25.1)	37 (16.4)
Asian	108 (5.3)	467 (3.3)	76 (2.4)	66 (2.6)	17 (2.3)	3 (1.3)
Multiracial/other	32 (1.5)	282 (1.9)	87 (2.9)	61 (2.4)	21 (2.9)	7 (3)

[a]$P < 0.05$ *vs* underweight.
[b]$P < 0.05$ *vs* healthy weight.
[c]$P < 0.05$ *vs* overweight.

[d]$P < 0.05$ *vs* obese I.
[e]$P < 0.05$ *vs* obese II.
[f]$P < 0.05$ *vs* obese III.
DGF: Delayed graft function; KDPI: Kidney Donor Profile Index.

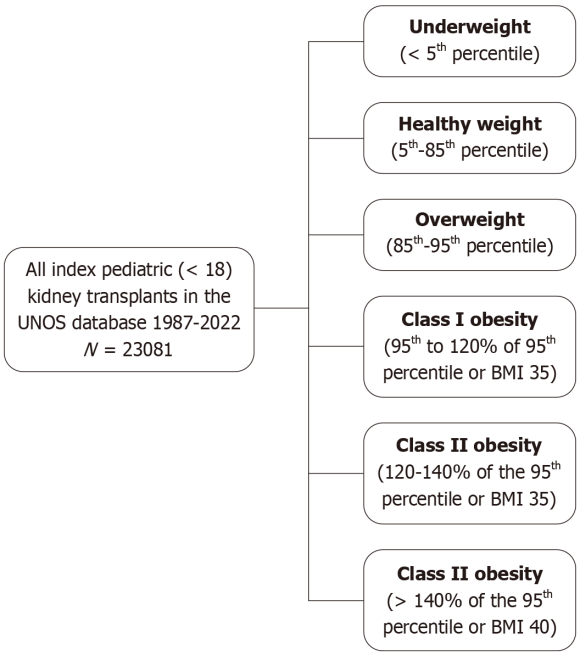

Figure 1 Representation of the separation of all pediatric kidney transplants into body mass index groups. BMI: Body mass index.

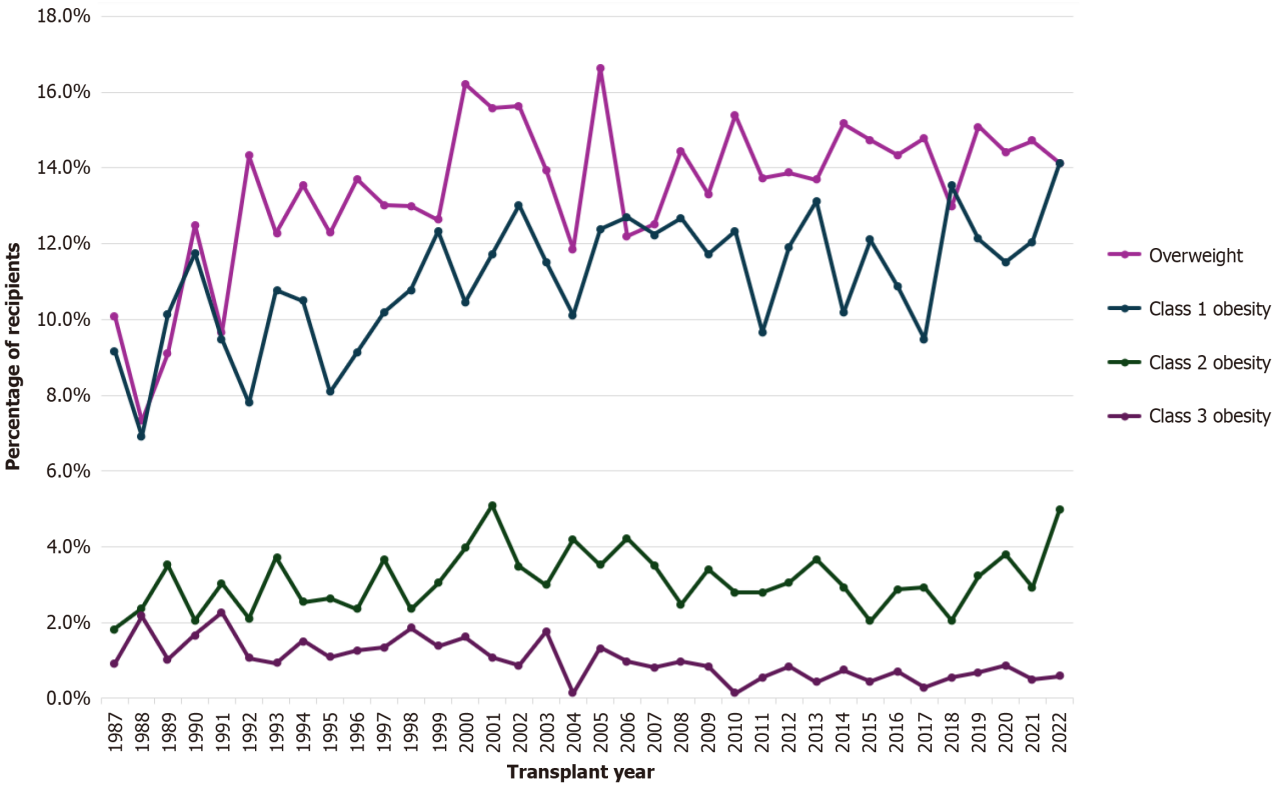

Figure 2 Line graph depicting trends in the percentage of overweight, obese I, obese II, and obese III pediatric recipients over time.

observed in long-term survival metrics. Underweight patients had significantly lower 10-year patient survival (81.3%) compared to healthy-weight patients (85.5%, $P = 0.003$), overweight (86.7%, $P = 0.003$), and Class 1 obese individuals (86.1%, $P = 0.001$) Class 2 obese patients had the lowest 10-year patient survival (78.9%) compared to healthy-weight (85.5%, $P < 0.001$) and overweight individuals (86.7%, $P < 0.001$). Similarly, Class 3 obese patients had significantly reduced 10-year survival (79.9%) compared to healthy-weight and overweight patients ($P < 0.05$) Kaplan-Meier analysis for graft survival and patient survival is depicted in Figure 3 and Figure 4. Log-rank testing, displayed in Table 2, revealed significantly lower graft survival in Class 2 ($P = 0.013$) and 3 (0.022) obese patients compared to healthy-weight individuals. This was similar when graft survival of Class 2 ($P = 0.033$) and Class 3 (0.033) obese patients were compared to Class 1 obese individuals. Similarly, significant differences in patient survival were observed comparing healthy weight to Class 2 ($P = 0.03$) and Class 3 ($P < 0.001$) obese groups over the study period. Underweight individuals had significantly lower graft survival than both healthy-weight individuals ($P = 0.007$) and overweight individuals ($P = 0.026$) in terms of patient survival (Table 3). No differences were seen between healthy-weight individuals and overweight ($P = 0.246$) and Class 1 Obese individuals ($P = 0.796$) in terms of graft survival. No differences were seen comparing healthy-weight individuals and overweight ($P = 0.845$) or Class 1 Obese individuals ($P = 0.179$) in terms of patient survival. Data from Cox regression identified key predictors of graft survival, this is depicted in Table 4. Each BMI point increase raised graft failure risk by 2.0% (95%CI: 1.015–1.025, $P < 0.001$). Older age increased graft failure risk by 4.1% per year (95%CI: 1.035–1.047, $P < 0.001$). Female recipients had a 14.5% higher risk of graft failure compared to males (95%CI: 1.090–1.204, $P < 0.001$). Later transplant eras reduced graft failure risk by 14.0% (95%CI: 0.845–0.875, $P < 0.001$). HLA mismatches and cold ischemic time also negatively impacted survival, increasing risk by 8.8% per mismatch unit (95%CI: 1.069–1.107, $P < 0.001$) and 1.1% per hour (95%CI: 1.008–1.013, $P < 0.001$), respectively. Ethnicity was not significant (95%CI: 0.998–1.002, $P = 0.887$). The impact of recipient diabetes was also negligible (95%CI: 1.000–1.000, $P = 0.059$). For patient survival, significant predictors included older age (4.9% higher mortality risk per year; 95%CI: 1.036–1.062, $P < 0.001$) and female gender (20.1% higher mortality risk compared to males; 95%CI: 1.087–1.327, $P < 0.001$). BMI category increases mortality risk by 1.8% (95%CI: 1.008–1.029, $P < 0.001$). Later transplant eras improved survival (95%CI: 0.871–0.940, $P < 0.001$). HLA mismatches and ischemic time further elevated risk by 11.9% per mismatch unit (95%CI: 1.080–1.160, $P < 0.001$) and 1.3% per hour (95%CI: 1.008–1.018, $P < 0.001$), respectively. Diabetes (95%CI: 1.000–1.001, $P = 0.155$) and ethnicity (95%CI: 0.999–1.003, $P = 0.370$) were not significant predictors.

DISCUSSION

This study highlights the impact of obesity on pediatric KT outcomes, providing insights into disparities across BMI categories. Our findings align with previous research suggesting that elevated BMI, particularly in Class 2 and 3 obesity, is associated with poorer transplant outcomes. Cox regression analysis identified obesity as an independent risk factor for both patient and graft survival, with each BMI point increase associated with a 2.0% higher hazard for graft failure (95%CI: 1.015-1.025, $P < 0.001$). While there were no significant differences in 1-year survival rates across BMI categories, underweight, Class 2, and Class 3 obese recipients demonstrated significantly lower 5- and 10-year survival rates compared to healthy-weight, overweight, and Class 1 obese individuals. These findings emphasize the risks associated with being underweight and with severe obesity. Longer CIT, a procedural factor in transplants, was more common amongst obese recipients, particularly those in Class 2 and 3 obesity. CIT independently increased the hazard of graft failure by 1.1% and patient mortality by 1.3% per additional hour. This is supported by previous findings that link prolonged CIT to worse graft and patient survival[14]. Living donor transplants, which are associated with shorter CIT and better survival, were significantly less common amongst overweight and obese recipients compared to their healthy counterparts[15,16]. This disparity is partially explained by parental obesity, as parents, who are the most likely living donors for their children, face BMI restrictions that could disqualify them from donating. Childhood obesity is directly linked to parental obesity, with children of obese parents being 3-6 times more likely to become obese themselves, and children with two obese parents are 10-12 times more likely[17]. The reasons for this are multifaceted, including genetic factors associated with fat storage and appetite, environmental factors including eating habits and lifestyles, alongside societal and familial pressures[17]. Although there is no national cut-off to be a kidney donor, most transplant centers will reject anyone over a BMI of 35, with some transplant centers rejecting anyone with a BMI of 30 and over. Addressing parental obesity through family-centered weight management programs before transplant could mitigate this barrier, increasing the availability of living donor kidneys for obese children. Obese pediatric recipients were more likely to be from non-White racial backgrounds, particularly Black and Hispanic populations, with Class 2 obesity showing the highest proportion of Black patients. Notably, ethnicity was not a significant predictor of either graft or patient survival after adjusting for other variables, including BMI, HLA mismatch, CIT, and transplant era. This finding supports the growing body of evidence that disparities in transplant outcomes among ethnic groups are driven by modifiable factors, including healthcare access, nutrition, and socioeconomic barriers rather than intrinsic biological differences[12]. Prior studies have shown no significant weight differences between Black and White preschool children when adjusting for prenatal, perinatal, and early life factors[18]. These results highlight the importance of addressing modifiable systemic barriers in improving transplant outcomes. Recipient age, gender, and transplant era also emerged as significant predictors of transplant outcomes. Older recipients experienced a 4.1% increased risk of graft failure and a 4.9% increased risk of mortality for each additional year of age, likely reflecting the cumulative impact of comorbidities, prolonged dialysis exposure, and immunological factors. Interestingly, male recipients, despite being more likely to be obese, demonstrated a 14.5% lower hazard of graft failure compared to females and 20.5 Lower hazard of mortality. This gender advantage may result from differences in fat distribution, hormones, immune responses, and medical treatment. In a

Table 2 Patient survival and graft survival log-rank testing between the different body mass index categories

Graft survival pairwise log rank testing	Underweight (< 5th)	Healthy weight (5th-85th)	Overweight (85th-95th)	Class 1 obese (95th-120%95th)	Class 2 obese (120%-140%95th)	Class 3 obese (> 140%95th)
Underweight (< 5th)		0.279	0.953	0.469	0.119	0.099
Healthy weight (5th-85th)	0.279		0.246	0.796	0.013	0.022
Overweight (85th-95th)	0.953	0.246		0.448	0.099	0.055
Class 1 obese (95th-120%95th)	0.469	0.796	0.448		0.033	0.033
Class 2 obese (120%-140%95th)	0.119	0.013	0.099	0.033		0.540
Class 3 Obese (> 140%95th)	0.099	0.022	0.055	0.033	0.540	
Patient survival pairwise log rank testing						
Underweight (< 5th)		0.007	0.026	0.316	0.779	0.013
Healthy Weight (5th-85th)	0.007		0.845	0.179	0.03	< 0.001
Overweight (85th-95th)	0.026	0.845		0.301	0.039	< 0.001
Class 1 obese (95th-120%95th)	0.316	0.179	0.301		0.235	0.002
Class 2 obese (120%-140%95th)	0.779	0.03	0.039	0.235		0.063
Class 3 obese (> 140%95th)	0.013	< 0.001	< 0.001	0.002	0.063	

Table 3 Median graft survival and median patient survival between the different body mass index categories

	Underweight (< 5th)	Healthy weight (5th-85th)	Overweight (85th-95th)	Class 1 obese (95th-120%95th)	Class 2 obese (120%-140%95th)	Class 3 obese (> 140%95th)
Median graft survival (95%CI) (years)	11.6 (10.9-12.3)[b,c,d,e,f]	12.2 (11.9–12.4)[a,e]	11.9 (11.4–12.4)[a,e]	12.0 (11.4–12.6)[a,e]	9.7 (8.7–10.6)[a,e]	11.8 (10.5–13.0)[a,b,c,d,e]
1-year graft survival rate	92.2%[f]	93.1%[f]	92.6%[f]	92.0%[f]	92.7%[f]	88.7%[a,b,c,d,e]
5-year graft survival rate	71.3%[b,c,d]	73.8%[a,e,f]	73.1%[a,e,f]	73.6%[a,e,f]	67.8%[b,c,d]	68.3%[b,c,d]
10-year graft survival rate	45.0%[b,c,d,f]	46.8%[a,e]	47.0%[a,e]	49.5%[a,e]	40.7%[b,c,d,f]	48.7%[a,e]
Median patient survival (95%CI) (years)	26.9 (24.4-29.4)[f]	26.0 (24.7-27.2)[f]	24.8 (23.6–25.9)[f]	24.8 (22.9-26.7)[f]		23.1 (21.1-25.0)[a,b,c,d]
1-year graft survival rate	92.2%	93.1%	92.6%	92.0%	92.7%	88.7%
5-year patient survival rate	93.6%[c,d]	92.5%[c,d]	95.6%[a,b,e,f]	94.6%[a,b,e,f]	92.6%[c,d]	91.3%[c,d]
10-year patient survival rate	81.3%[b,c,d]	85.5%[a,e,f]	86.7%[a,e,f]	86.1%[a,e,f]	78.9%[b,c,d]	79.9%[b,c,d]

[a]$P < 0.05$ *vs* underweight.
[b]$P < 0.05$ *vs* healthy weight.
[c]$P < 0.05$ *vs* overweight.
[d]$P < 0.05$ *vs* obese I.
[e]$P < 0.05$ *vs* obese II.
[f]$P < 0.05$ *vs* obese III.

majority of high and upper-middle-income countries, boys are more often obese, influenced by biological factors including leptin levels and societal pressures on girls to maintain a lower body weight[19]. Successive transplant eras were associated with significant improvements in survival, with each era reducing the hazard of graft failure by 14.0% and mortality by 9.5%. This is also multifaceted, impacted by advances in surgical techniques that have minimized perioperative complications, improved immunosuppressive regimens with more efficacious medications, and changes in

Table 4 Predictors of graft and patient survival based on cox regression analysis

Predictor	Hazard ratio	95%CI	*P* value
BMI (per point)	1.020	1.015–1.025	< 0.001
Age (per year)	1.041	1.035–1.047	< 0.001
Female gender (*vs* male)	1.145	1.090–1.204	< 0.001
Transplant era (per later era)	0.860	0.845–0.875	< 0.001
HLA mismatch (per unit)	1.088	1.069–1.107	< 0.001
Cold ischemia time (per hour)	1.011	1.008–1.013	< 0.001
Ethnicity	1.000	0.998–1.002	0.887
Presence of diabetes	1.000	1.000–1.000	0.059
BMI (per point)	1.049	1.036–1.062	< 0.001
Age (per year)	1.201	1.087–1.327	< 0.001
Female gender (*vs* male)	1.018	1.008–1.029	< 0.001
Transplant era (per later era)	0.905	0.871–0.940	< 0.001
HLA mismatch (per unit)	1.119	1.080–1.160	< 0.001
Cold ischemia time (per hour)	1.013	1.008–1.018	< 0.001
Ethnicity	1.001	0.999–1.003	0.370
Presence of diabetes	1.000	1.000–1.001	0.155

BMI: Body mass index.

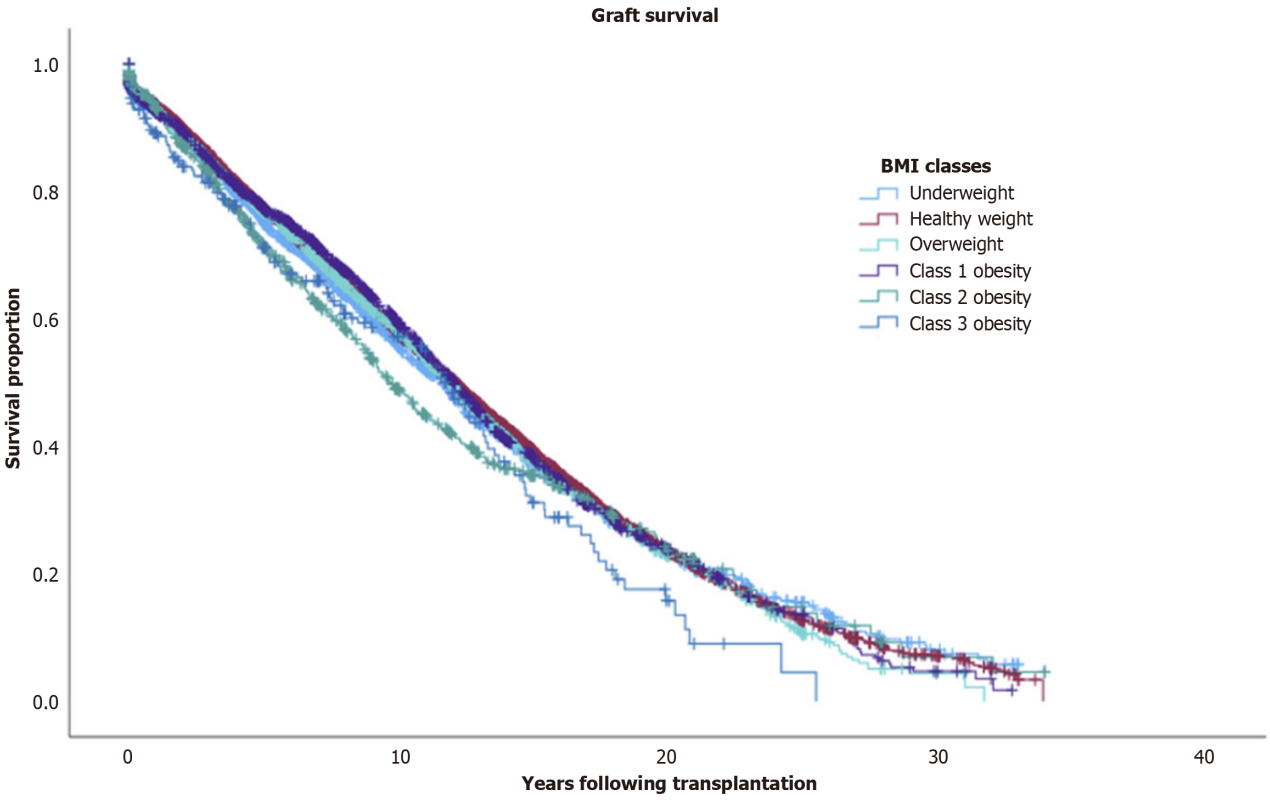

Figure 3 Kaplan-Meier estimates of kidney allograft survival between body mass index classes. Correlate statistically significant differences in graft survival between body mass index classes using the log-rank testing in Table 2. BMI: Body mass index.

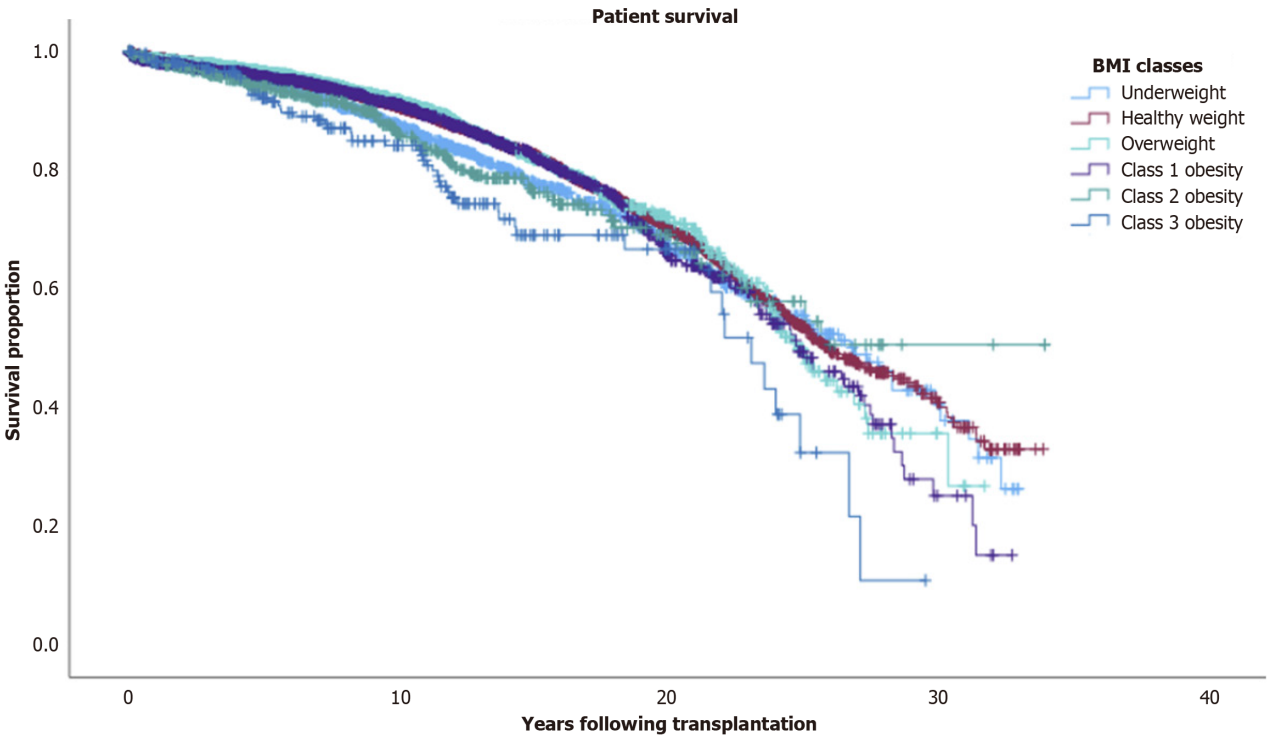

Figure 4 Kaplan–Meier estimates of kidney allograft recipient survival between the different body mass index classes. Correlate statistically significant differences in patient survival between body mass index classes using the log-rank testing in Table 2.

pediatric allocation policy. The 2014 revision to the Kidney Allocation System introduced a system in which pediatric candidates received priority for all kidneys with a KDPI < 35%[20]. This change increased long-term survival outcomes by improving access to high-quality grafts[20]. Underweight recipients demonstrated lower survival rates compared to their normal-weight counterparts, highlighting the dual risks of obesity and malnutrition (Table 2). Previous studies have shown that underweight pediatric KT recipients face an increased risk of mortality secondary to cardiovascular disease when compared to normal-weight patients[21]. Large annual decreases in BMI have similarly shown increased mortality risk in children treated with KT[22,23]. Nutritional management should prioritize stabilizing BMI within a healthy range, recognizing that BMI serves as both an indicator of obesity and a marker of malnutrition or severe illness. No significant differences were observed between BMI groups in other important transplant metrics, such as donor distance from the transplant center, KDPI, donor sex, or rates of DGF. This suggests that the primary factors contributing to poorer outcomes in obese pediatric recipients are related more to recipient characteristics than donor variables. Additionally, although there was a trend in DGF rates, which increased proportionally with BMI, it was insignificant in our data, suggesting a potential area for future study within other datasets. Barriers to healthcare disproportionately impact low-income families and families of color, exacerbating disparities in transplant outcomes. Black Americans represent 31.9% of KT candidates but account for only 11.7% of living donors, a disparity driven by socioeconomic factors, healthcare mistrust, and lack of awareness about organ donation[24,25]. Financial assistance programs and culturally competent transplant teams are essential to building trust and reducing economic barriers, with pilot programs showing early success in increasing minority living donor transplants[25]. Public health initiatives targeting systemic inequalities, such as improving access to nutritious food and obesity prevention programs, could further address disparities in pediatric KT [26]. Despite the well-documented risks associated with obesity, particularly in the context of KT, this study suggests that with the proper management, obese pediatric patients can still achieve comparable outcomes to their healthy-weight counterparts in the short term. Given the comparable outcomes in overweight and Class 1 obese children in the setting of more obese and overweight children presenting for transplant than ever before, it seems as if the American transplant system has already adjusted to the trends in pediatric BMI. However, the long-term outlook, particularly for those in Class 2 and 3 obesity, remains concerning, with lower graft survival at 5 and 10 years. Structured pre-transplant interventions, such as comprehensive weight management programs, are an important addition to transplant teams. Programs integrating dietary counseling, behavioral therapy, and physical activity have successfully reduced BMI in pediatric population[27]. In severe cases, bariatric surgery has been shown to improve outcomes with obesity-related comorbidities, but there has not been extensive work on how it would impact pediatric transplant recipients[28]. Post-transplant interventions, including regular follow-ups with dietitians and physical activity programs, would allow for progress to be sustained over time, ultimately improving graft and patient survival. Emerging therapies like GLP-1 receptor agonists, which are effective in managing obesity and associated metabolic conditions, may offer a promising adjunct for improving outcomes in obese pediatric KT recipients. By promoting weight loss and improving insulin sensitivity, these agents could help optimize pre- and post-transplant health, potentially mitigating obesity-related risks. Further research is needed to explore their safety, efficacy, and long-term impact in this unique population. This study underscores the need for nuanced criteria in assessing and treating pediatric KT candidates with elevated BMI. While

some transplant centers may view obesity as an absolute contraindication, our findings suggest that blanket restrictions on BMI alone may be too conservative. Instead, transplant centers should consider adopting a more individualized approach that considers a patient's overall health and management of the patient's obesity before and after transplant. Additionally, efforts to reduce barriers to living donor transplants for obese patients, including support for obese parents attempting child-parent donations, could reduce some of the risks faced by obese pediatric recipients.

This study, while comprehensive with an extensive number of transplants, has several limitations. First, the retrospective cohort design precludes the ability to establish causation between BMI and transplant outcomes. While the findings suggest associations between higher BMI categories and poorer graft and patient survival, the observational nature of the study means that unmeasured confounding factors may influence these outcomes. Additionally, the STAR/UNOS database lacks granular information about potential confounders, such as recipient hypertension, socioeconomic factors, and detailed metrics on obesity-related comorbidities, all of which could influence the data. Finally, the relatively small number of Class 3 obese patients may reduce the statistical power for this subgroup and limit the generalizability of the findings. The definition of Class 3 obesity (140% of the 95th percentile or BMI = 40) inherently encompasses a small fraction of the pediatric population, and a multi-center study focused on these patients would be needed to validate findings in this subgroup. Further prospective studies with more detailed clinical data are required to better understand causal relationships between BMI and outcomes in pediatric KT.

CONCLUSION

This study highlights the complex relationship between obesity and pediatric KT outcomes, emphasizing that Class 2 and 3 obesity are associated with significantly poorer long-term graft and patient survival. Cox regression analysis identified obesity and longer cold ischemic times as independent risk factors, with each BMI point increase associated with higher hazards for graft failure and mortality. However, recipients in the overweight and Class 1 obesity categories demonstrated comparable short-term and long-term outcomes to their healthy-weight counterparts, demonstrating the potential for clinical success with proper management. The disproportionate impact of obesity on Black and Hispanic children, alongside barriers to living donor transplants due to parental obesity, highlights the need for systemic interventions. Family-centered weight management programs to address both pediatric and parental obesity could expand the pool of eligible living donors and improve access to higher-quality organs. Pre- and post-transplant strategies, including dietary counseling, behavioral therapy, and physical activity programs, are important to optimize outcomes.

FOOTNOTES

Author contributions: Stanicki B and Puntiel DA led the study design, participated in data analysis, performed statistical analysis in conjunction with the Temple University Center for Biostatistics and Epidemiology and drafted and finalized the manuscript; Peticca B participated in design and oversight of the study and assisted with the data analysis; Egan Nicolas, Prudencio TM, and Robinson SG participated in data analysis and drafting the manuscript; Karhadkar SS participated in oversight of the study, drafted, and finalized the manuscript; all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Clinicopathological characteristics and long-term outcomes of adult patients with proliferative lupus nephritis

Saima Ahmed, Tabassum Elahi, Muhammed Mubarak, Ejaz Ahmed

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Abstract

BACKGROUND

Proliferative lupus nephritis (PLN) is the most severe form of lupus nephritis (LN). There are limited data available on renal outcomes of PLN from developing countries.

AIM

To determine the clinicopathological characteristics and long-term outcomes in terms of remission, requirement of kidney replacement therapy (KRT), and patient survival.

METHODS

A retrospective analysis was conducted on biopsy-proven focal or diffuse PLN cases diagnosed between 1998 and 2019 at the Sindh Institute of Urology and Transplantation and followed up at the renal clinic for a minimum of 5 years. All patients were induced with a combination of intravenous cyclophosphamide and corticosteroids for 6 months, followed by maintenance treatment with azathioprine (AZA) or mycophenolate mofetil (MMF). Data were analyzed using Statistical Package for the Social Sciences, version 22.0. $P \leq 0.05$ was considered statistically significant.

RESULTS

The mean age at the onset of systemic lupus erythematosus was 24.12 years ± 8.89 years, and at LN onset, 26.63 years ± 8.61 years. There was a female predominance of 184 (88.9%) cases. Among baseline characteristics, reduced estimated glomerular filtration rate, presence of hypertension, requirement of KRT, and underlying renal histology (International Society of Nephrology/Renal Pathology Society class IV than class III) were significantly associated with end-stage kidney

disease (ESKD) and mortality. The renal outcomes were negatively correlated with age, duration of symptoms, and 24-hour urinary protein excretion. The overall remission rate was 89.8% at the end of induction therapy. At 5 years, 141 (68.11%) patients were in complete and partial remission (94 [45.4%] and 47 [22.7%], respectively). In total, 19 (9.2%) patients required KRT on presentation, and at 5 years, 38 (18.4%) patients developed ESKD, and 28 (13.5%) patients died. Thirty-four (16.4%) patients had a renal relapse, more with AZA than MMF (30 [88.2%] *vs* 4 [11.76%], respectively; $P = 0.04$). Renal survival at 6 months was 89.8%, while at 5 years, it was 68.11%, showing a significant improvement in patients who did not need KRT at the time of presentation ($P < 0.0001$).

CONCLUSION

Baseline renal functions, requirement of KRT, and diffuse proliferative disease were the most relevant prognostic factors for kidney survival among this cohort. Short-term renal outcomes were good. Long-term outcomes were poorer with AZA-based maintenance therapy than with MMF, with more ESKD and mortality.

Key Words: Systemic lupus erythematosus; Lupus nephritis; Proliferative lupus nephritis; Estimated glomerular filtration rate; End-stage kidney disease; Kidney replacement therapy

Core Tip: Lupus nephritis (LN) presents significant variability in clinical manifestations and treatment response. Although current treatments have markedly improved outcomes for patients with proliferative LN (PLN), a significant number of patients still gradually progress to end-stage kidney disease. There is still a lack of understanding about the factors that affect therapy non-response and the survival rates of patients with PLN, particularly from developing countries. This study aims to bridge these gaps, enhancing understanding of outcome disparities between developed and developing countries.

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INTRODUCTION

One of the gravest forms of systemic lupus erythematosus (SLE) is lupus nephritis (LN), which affects the kidneys. About 38% of individuals with SLE experience renal complications, with a prevalence ranging from 12% to 69%, influenced by factors such as ethnicity, sex, and age of onset[1]. Among Black individuals, a higher frequency, earlier onset, and poorer prognosis have been documented[2,3]. Conversely, renal involvement in European populations is reportedly 27.9%[4]. There is significant variability among Asian countries, with rates ranging from 18% to 100% but predominantly exceeding 50%[5].

LN is currently classified histopathologically into classes I to VI, based on the 2003 classification system by the International Society of Nephrology/Renal Pathology Society (ISN/RPS)[6], over half of the patients are affected by proliferative LN (PLN)[6], which includes either class III or class IV, either alone or in combination with class V. This condition includes both focal and diffuse disease, leading to a higher risk of mortality and affecting both short- and long-term renal survival. Consequently, for patients with PLN, aggressive immunosuppressive therapy is suggested to enhance renal outcomes. This approach has resulted in a global 10-year renal survival rate of nearly 90%[7]. Caucasians generally show a better response and more favorable long-term outcomes compared to more ethnically diverse populations in the United States and Asia[8,9].

Patients with LN exhibit a wide spectrum of clinical presentations, from subtle urinary irregularities to severe, symptomatic cases of nephritic syndrome or swiftly advancing renal failure[10]. It is an important cause of chronic kidney disease (CKD) and mortality[11,12]. Despite advancements in treatment strategies and improved patient survival over recent decades, 10%-20% of patients still progress to end-stage kidney disease(ESKD) within the first 10 years of their disease course[13,14]. Therefore, early prediction of long-term renal outcomes is crucial.

Discrepant renal outcomes have been reported across various Asian studies, potentially due to differences in sample size, time between symptom onset and treatment initiation, histological classifications (classes III, IV, and V lesions), remission criteria, treatment regimens, follow-up durations, relapses, and flares[15-17]. Better survival rates have been linked to timely referrals to nephrologists, heightened awareness, the success of new induction regimens, and overall advancements in medical care. As a result, the management objectives for PLN can be divided into short-term goals (preventing flares) and long-term aims (preserving renal function)[18-20]. The initiation of induction therapy with cyclophosphamide (CYC) has improved patient survival, with a 5-year survival rate of 82% for class IV LN[21].

Although extensive research on LN treatment outcomes and survival has been conducted in developed countries, the issue remains underexplored in developing nations. Despite the higher prevalence of LN in Asian countries compared to Europe, data from South Asian countries, particularly Pakistan, is scarce. A study by Rabbani *et al*[22] reported the

frequency of renal involvement among Pakistani patients with SLE and those who progressed to ESKD in 2009[23]. Since then, no comprehensive data on renal outcomes, whether short- or long-term, has been published from Pakistan. Further research is needed to understand the factors related to therapy non-response and the survival outcomes of patients with LN, particularly those with PLN.

Hence, the current study aimed to address these gaps in knowledge by determining the clinicopathological characteristics and long-term outcomes in patients with PLN.

MATERIALS AND METHODS

Ethics statement

The present study was approved by the institutional review board of the Sindh Institute of Urology and Transplantation (SIUT) (SIUT-ERC-2020/A-227; Karachi, Pakistan). The research was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study population

A retrospective review was conducted on the medical records of all adults over 18 years old who were referred to the renal division of SIUT in Karachi, Pakistan, with a serological and histopathological diagnosis of PLN from January 1998 to December 2019. These patients were followed up at the renal clinic for at least 5 years after their renal biopsy.

Data collection

The medical records of all adult patients diagnosed with PLN were examined for various clinical, biochemical, serological, and histopathological parameters at initial presentation and during subsequent follow-ups at the renal clinic. Clinical information reviewed included age at SLE diagnosis and renal biopsy, sex, history of constitutional symptoms, oliguria, duration of symptoms prior to admission, a comprehensive review of extra-renal manifestations, and physical examination findings such as hypertension, edema, rash, and other pre-biopsy signs. Additionally, the records detailed the treatment regimens administered, the necessity for kidney replacement therapy (KRT), and follow-up data spanning a minimum of 5 years.

Laboratory parameters such as serum creatinine and albumin levels were recorded both at presentation and during follow-up visits. Serum complement levels (complement component 3 [C3] and C4) were noted and categorized as low or normal. Additionally, detailed urine reports, urine protein creatinine ratio (PCR) upon arrival and subsequently, and 24-hour urinary protein levels (if available) were documented. The estimated glomerular filtration rate (eGFR) was calculated using the CKD epidemiology collaboration creatinine equation[24].

Classification and histopathology

The histological assessment included evaluating the total number of glomeruli, the number of sclerosed glomeruli, and the number and proportion of glomeruli with crescents. These crescents were further classified into cellular, fibrocellular, and fibrous types. Other parameters included mesangial hypercellularity (either diffuse or focal), endocapillary hypercellularity, capillary wall double contours, and the extent of interstitial fibrosis and tubular atrophy, which were semi-quantitatively graded as none (0%), mild (6%-25%), moderate (26%-50%), or severe (> 50%). Additionally, immunofluorescence (IF) was used to detect the presence of immunoglobulin A (IgA), IgG, IgM, C3, C1q, κ, and λ, with their staining patterns and intensity rated on a scale from 0 to 3+ (0: No staining; 1+: Mild; 2+: Moderate; and 3+: Severe).

Treatment protocol

Patients with PLN (classes III and IV, with or without class V) underwent induction therapy with intravenous (IV) methylprednisolone at a dose of 0.5-1 g/day for 3 days, followed by oral prednisolone according to the department's protocol. Prednisolone was initially administered at 1 mg/kg/day for 4 to 8 weeks and then gradually tapered by 10 mg every 2 weeks to reach a maintenance dose of 5 mg/day to 10 mg/day within 4 to 6 months. All patients also received IV CYC according to the National Institutes of Health regimen[25], which consisted of monthly pulses of 500-1000 mg/m² of body surface area for 6 months. This was followed by maintenance therapy with prednisolone (5-10 mg/day) and either azathioprine (AZA) at 2 mg/kg or mycophenolate mofetil (MMF) at 1-2 g/day, as determined by the treating clinicians. Notably, MMF was not used as induction therapy in this study. Patients with mixed PLN were treated with a similar regimen. Hydroxychloroquine at a dose of 200–400 mg was administered to all patients unless contraindicated or restricted by financial constraints.

PLN was defined as classes III and IV LN, while classes II and V were designated as non-proliferative LN.

Outcomes

Complete remission (CR) was characterized by normal urinalysis results (dipstick negative or trace for both proteins and blood), serum albumin levels above 3.5 g/dL, and an eGFR greater than 90 mL/minute/1.73 m².

Partial remission (PR) was identified by abnormal urinalysis findings, such as microscopic hematuria or ≥ 1 proteinuria, serum albumin levels below 3.5 g/dL, and an eGFR ranging from 60 mL/minute/1.73 m² to 90 mL/minute/1.73 m².

No remission was defined as persistent proteinuria of more than 3 g/day or progressive or worsening renal function.

Renal survival was measured as the duration from renal biopsy to the occurrence of any of these events: (1) Initiation of dialysis; (2) Receiving a kidney transplant; and (3) eGFR dropping below 15 mL/minute/1.73 m² at any point during follow-up and not returning above 15 mL/minute/1.73 m² in subsequent checks.

Renal relapse was defined as the reappearance of a positive dipstick (after previously being negative) or an increase in proteinuria (evident on dipstick or an increase in PCR) in patients who had achieved PR or CR.

Study endpoints

The main objective was to measure renal survival, which was characterized by the absence of ESKD or death. The secondary objective focused on evaluating the rate of PR or CR during the follow-up period.

Statistical analyses

The data analysis was conducted using the Statistical Package for the Social Sciences, version 22.0 (IBM Corp, Armonk, NY, United States). Continuous data are presented as the mean ± SD or median with interquartile range. Categorical data are displayed as numbers and percentages, while discrete data are shown as proportions. Differences in means and proportions were assessed using analysis of variance (ANOVA) for continuous variables and the χ^2 test for categorical variables. Overall survival curves were generated using the Kaplan–Meier method, and differences between these curves were evaluated using a log-rank test. $P < 0.05$ was considered statistically significant.

RESULTS

From 1998 to 2019, a total of 207 patients were diagnosed with biopsy-confirmed PLN. Among these, 103 patients (49.8%) exhibited ISN/RPS histology class IV, while 43 patients (20.8%) were classified as class III. The remaining 30% of patients had mixed PLN with class V.

Patient demographics and clinical parameters at the time of presentation

Table 1 provides an overview of the demographic, clinical, and serological features of patients diagnosed with PLN. The average age at SLE onset was 24.12 years ± 8.89 years, whereas the average age at LN onset was 26.63 years ± 8.61 years. The interval between the onset of SLE and LN averaged 12.21 months ± 14.58 months. Females were dominant comprising 184 (88.9%) patients, while there were 23 (11.1%) male patients. Hypertension was present in 126 (60.9%) patients. Extra-renal manifestations included constitutional symptoms (98.6%), rash (78.3%), polyarthalgia/arthritis (97.6%), lung involvement (24.2%), and central nervous system–associated symptoms (18.4%). A total of 144 (69.56%) patients exhibited nephrotic range proteinuria in conjunction with microscopic hematuria. The average eGFR was 75.21 mL/minute/1.73 m² ± 42.59 mL/minute/1.73 m². On presentation, 25 (12.1%) patients were oliguric, of whom 19 (9.2%) patients required KRT. A total of 138 (66.7%) patients showed C4 complement consumption; 133 (64.3%) patients were on immunosuppression prior to renal biopsy; and 144 (69.56%) patients received maintenance treatment with AZA, while the remaining 63 (30.4%) patients were treated with MMF.

Renal histopathological features

Table 2 shows the renal histopathological features of patients diagnosed with PLN. The predominant histological pattern identified was diffuse proliferative glomerulonephritis (76.32%), either occurring alone or in conjunction with class V. Extracellular crescentic proliferation was detected in 74 patients, accounting for 35.7% of the cohort. The average proportion of sclerotic glomeruli was 1.31 ± 2.60, which corresponded to 6.69%. A total of 154 (74.39%) biopsies had mild or no tubular atrophy. The complete full house pattern on IF was observed in 80% of the patients.

Renal outcomes

Table 3 illustrates renal functional parameters during the 5 years of follow-up. After 6 months of induction therapy, 186 (89.8%) patients had achieved CR and PR (64 [30.9%] and 122 [58.9%], respectively). Seven (3.4%) were dialysis-dependent, and fourteen (6.8%) patients died. Patients who did not require KRT at the time of admission had a higher rate of CR and PR, with 62 patients (32.97%) achieving CR compared to 2 patients (10.52%) ($P = 0.04$), and 113 patients (60.1%) achieving PR compared to 9 patients (47.36%) ($P = 0.28$). Moreover, fewer patients in this group progressed to ESKD, with 4 patients (2.12%) compared to 3 patients (15.7%) ($P = 0.002$). Additionally, mortality was lower in this group, with 9 patients (4.78%) dead in this group compared to 5 patients (26.3%) in the group requiring KRT ($P < 0.001$).

At the 5-year mark, a total of 141 patients (68.11%) achieved either CR or PR, with 94 patients (45.4%) in CR and 47 patients (22.7%) in PR. During this period, 38 patients (18.4%) progressed to ESKD, and 28 patients (13.52%) passed away. Among those requiring KRT at admission, fewer attained CR and PR, with 3 patients (15.7%) reaching CR compared to 91 patients (48.40%) ($P = 0.005$) and 2 patients (10.52%) achieving PR compared to 45 patients (23.9%) ($P = 0.17$). Additionally, a higher proportion of these patients progressed to ESKD, with 8 patients (42.10%) compared to 30 patients (15.95%) ($P = 0.002$), and mortality was higher, with 6 patients (31.57%) compared to 22 patients (11.7%) ($P = 0.016$).

During the 5-year follow-up period, 34 patients (16.4%) experienced renal relapses, all of whom did not require KRT at presentation. Of these patients, 23 (11.1%) underwent re-biopsy. The relapse rate was higher among patients treated with AZA, with 30 patients (88.2%), compared to those treated with MMF, with 4 patients (11.76%).

Kaplan-Meier survival analysis was performed, considering the period from treatment initiation to the end of follow-up or death as the timeframe. Renal survival was 89.8% at 6 months and 68.11% at 5 years (Figure 1A). The survival rate

Table 1 Baseline demographic and clinical characteristics of patients with proliferative lupus nephritis, *n* (%)

	***n* = 207**
Age at systemic lupus erythematosus diagnosis (years), mean ± SD	24.12 ± 8.89
Age at renal biopsy (years), mean ± SD	26.63 ± 8.61
Sex	
Male	23 (11.1)
Female	184 (88.9)
Weight (kg), mean ± SD	51.47 ± 11.97
Duration between onset of symptoms and biopsy (months), mean ± SD	12.21 ± 14.58
Hypertension	126 (60.9)
Oliguria at presentation	25 (12.1)
Macroscopic hematuria	3 (1.4)
Edema	44 (64.7)
Constitutional symptoms	204 (98.6)
Sinus/ENT	3 (1.4)
Skin rash/purpura	162 (78.3)
Lung involvement	50 (24.2)
Arthritis/polyarthalgia	202 (97.6)
Neurological	38 (18.4)
Renal biopsy International Society of Nephrology/Renal Pathology Society classification	
III	43 (20.8)
IV	103 (49.8)
III/IV	6 (2.9)
III/V	5 (2.4)
IV/V	50 (24.2)
Antiphospholipid syndrome positive	20 (9.7)
Extractable nuclear antigen positive	20 (9.7)
Proteinuria (dipstick)	
1+	9 (4.3)
2+	50 (24.2)
3+	119 (57.5)
4+	25 (12.1)
Microscopic hematuria	
Trace	38 (18.4)
1+	31 (15)
2+	44 (21.3)
3+	66 (31.9)
4+	14 (6.8)
Serum creatinine (mg/dL), mean ± SD	1.67 ± 1.79
Estimated glomerular filtration rate (mL/minute/1.73 m²), mean ± SD	75.21 ± 42.59
Serum albumin (g/dL), mean ± SD	2.30 ± 0.62
Spot protein creatinine ratio (g/dL) or 24 hours urinary protein (g/day), mean ± SD	3.54 ± 3.13
Serum C3 levels	

Low (< 0.8)	171 (82.6)
Normal (> 0.8)	36 (17.4)
Serum C4 levels	
Low (< 0.16)	138 (66.7)
Normal (> 0.16)	69 (33.3)
Kidney replacement therapy on admission	19 (9.2)
Immunosuppression before biopsy	133 (64.3)
Maintenance treatment	
Azathioprine	144 (69.56)
Mycophenolate mofetil	63 (30.43)
Hydroxychloroquine	131 (63.28)

ENT: Ear, nose, and throat; SD: Standard deviation.

Table 2 Histopathological characteristics in patients with proliferative lupus nephritis, *n* (%)

	***n* = 207**
Total glomeruli ± SD	19.43 ± 7.39
Globally sclerosed ± SD	1.31 ± 2.60
Presence of crescents	74 (35.7)
Mesangial/endocapillary proliferation	
Focal	49 (23.67)
Diffuse	158 (76.32)
Interstitial fibrosis/tubular atrophy	
None	43 (20.7)
Mild	111 (53.62)
Moderate	38 (18.35)
Severe	3 (1.44)
IgA	133 (64.3)
IgG	164 (79.2)
IgM	160 (77.3)
C3	180 (87)
C1q	160 (77.3)

C1q: Complement component 1q; C3: Complement component 3; Ig: Immunoglobulin; SD: Standard deviation.

was significantly better in patients who did not require KRT at presentation ($P < 0.001$) (Figure 1B).

Comparison of renal outcomes and baseline mean clinicopathological characteristics

To evaluate the mean baseline values of parameters in different patient categories such as CR, PR, ESKD, and mortality, an ANOVA test was performed to compare their responses to treatment. It was found that age, duration between onset of symptoms and biopsy, and degree of proteinuria had no significant correlation with the outcomes. The outcomes showed a strong correlation with the presence of hypertension, baseline eGFR, the need for KRT at the time of admission, and renal histology. Patients who achieved CR had a lower incidence of hypertension, with 40 patients (42.5%) affected, and demonstrated higher eGFR values, averaging 90.27 mL/minute/1.73 m² ± 30.08 mL/minute/1.73 m², than those patients with PR (71.62 mL/kg/m² ± 40.29 mL/kg/m²), ESKD (56.31 mL/kg/m² ± 44.96 mL/kg/m²), and died (60.25 mL/kg/m² ± 41.68 mL/kg/m²) ($P < 0.001$). Similarly, fewer patients required KRT on admission in patients with CR (3 [3.19%]) and PR (2 [4.25%]) than those who progressed to ESKD (8 [21.05%]) and died (6 [21.42%]) ($P = 0.001$). Patients with fewer globally sclerosed glomeruli, fewer crescents (30 [31.9%]), focal proliferation, and mild to no tubular atrophy (87.6%)

Table 3 5-year renal outcomes in patients with and without requirement of kidney replacement therapy on presentation, *n* (%)

	Overall (*n* = 207)	Required KRT on presentation (*n* = 19)	Not required KRT on presentation (*n* = 188)	*P* value
Renal outcomes after induction with pulse cyclophosphamide at 6 months				
CR	64 (30.9)	2 (10.52)	62 (32.97)	0.04
PR	122 (58.9)	9 (47.36)	113 (60.1)	0.28
ESKD	7 (3.4)	3 (15.7)	4 (2.12)	0.002
Mortality	14 (6.8)	5 (26.3)	9 (4.78)	0.000
Final outcomes at 5 years				
CR	94 (45.4)	3 (15.7)	91 (48.40)	0.005
PR	47 (22.7)	2 (10.52)	45 (23.9)	0.170
ESKD	38 (18.35)	8 (42.10)	30 (15.95)	0.010
Mortality	28 (13.52)	6 (31.57)	22 (11.7)	0.016
Renal relapses during 5-year follow-up	34 (16.4)	0	34 (18.0)	0.043
Azathioprine	30 (88.2)	0	30 (88.2)	
Mycophenolate mofetil	4 (11.76)		4 (11.76)	
Re-biopsy	23 (11.1)	1 (5.2)	22 (11.70)	0.67

CR: Complete remission; ESKD: End-stage kidney disease; KRT: Kidney replacement therapy; PR: Partial remission.

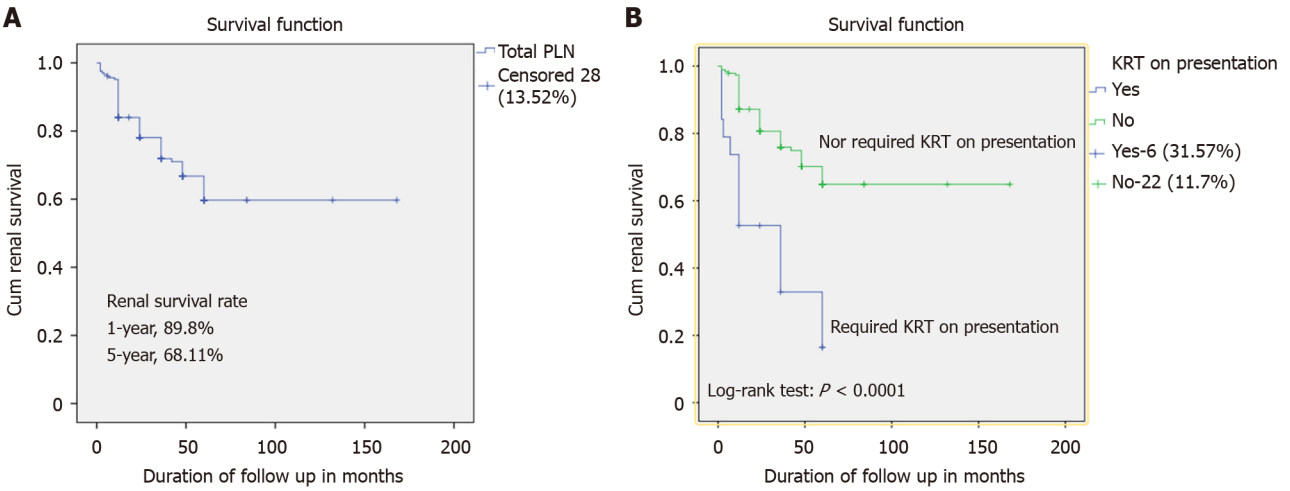

Figure 1 Kaplan-Meier curves. A: Kaplan-Meier curves showing overall 1-year and 5-year renal survival; B: Kaplan–Meier survival analysis of proliferative lupus nephritis patients on follow-up stratified by requirement of kidney replacement therapy (KRT) on presentation. PLN: Proliferative lupus nephritis.

observed through light microscopy, experienced higher rates of CR and PR ($P < 0.001$). These findings are detailed in Table 4.

DISCUSSION

LN is a highly heterogeneous disease with variable treatment responses. Despite advancements in current treatments, many patients with PLN still progress to ESKD. This study provides a comprehensive analysis of treatment outcomes, survival status, and associated factors for PLN patients in the South-Asian context, specifically from Pakistan. Despite being a single-center study, it is one of the largest studies to thoroughly assess various factors impacting PLN treatment outcomes and survival rates, utilizing a relatively large sample size.

Table 4 Comparison between renal outcomes and baseline mean values of clinicopathological characteristics by using analysis of variance test, *n* (%)

Variable	Complete remission (*n* = 94)	Partial remission (*n* = 47)	End-stage kidney disease (*n* = 38)	Mortality (*n* = 28)	*P* value
Age (years), mean ± SD	26.21 ± 45 7.54	27.89 ± 11.05	25.87 ± 7.98	26.14 ± 8.37	0.699
Duration between onset of symptoms and biopsy (months), mean ± SD	10.98 ± 13.94	11.79 ± 10.85	16.63 ± 21.44	11.07 ± 9.40	0.225
Hypertension	40 (42.5)	31 (65.95)	13 (34.21)	24 (85.71)	< 0.0001
Serum creatinine (mg/dL), mean ± SD	1.14 ± 0.82	1.49 ± 1.01	2.54 ± 2.50	2.59 ± 2.99	< 0.0001
Serum albumin on admission (g/dL), mean ± SD	2.42 ± 0.70	2.32 ± 0.55	2.05 ± 0.44	2.16 ± 0.50	0.014
Protein creatinine ratio (g/dL), mean ± SD	3.27 ± 2.82	4.17 ± 3.94	3.05 ± 2.26	4.16 ± 3.71	0.45
Estimated glomerular filtration rate (mL/minute/1.73 m²) mean ± SD	90.27 ± 30.08	71.62 ± 40.29	56.31 ± 44.96	60.25 ± 41.68	< 0.0001
Required kidney replacement therapy on admission	3 (3.19)	2 (4.25)	8 (21.05)	6 (21.42)	0.001
Mesangial/endocapillary proliferation					
Focal	33 (35.10)	11 (23.40)	4 (10.52)	1 (3.571)	0.001
Diffuse	61 (64.89)	36 (76.59)	34 (89.47)	27 (96.42)	
Number of globally sclerosed glomeruli, mean ± SD	0.55 ± 1.2	1.44 ± 2.22	2.62 ± 4.05	1.80 ± 3.21	< 0.0001
Presence of crescents	30 (31.9)	18 (38.29)	15 (39.47)	11 (39.28)	0.010
Interstitial fibrosis/tubular atrophy					< 0.0001
None	36 (38.29)	4 (8.51)	2 (5.26)	2 (7.14)	
Mild	49 (52.12)	30 (63.8)	22 (57.89)	10 (35.7)	
Moderate	9 (9.57)	13 (27.65)	14 (36.8)	12 (42.85)	
Severe	0	0	0	4 (14.2)	

SD: Standard deviation.

In this study, baseline clinical and laboratory variables showed no correlation between outcomes and age, symptom duration, or 24-hour urinary protein, aligning with findings by Aliyi *et al*[26]. While proteinuria reduction serves as a marker for renal outcomes, our study identified significant predictors of outcomes, including reduced baseline eGFR, presence of hypertension, need for KRT at presentation, underlying renal histology (ISN/RPS class IV compared to class III), increased globally sclerosed glomeruli, presence of crescents, and moderate to severe IF/TA. These results are consistent with Dhir *et al*[27] from India.

In the current study, we observed that the overall remission at the end of induction therapy was 89.8%: (1) CR in 30.9 % of patients; and (2) PR in 58.9% of patients. This finding aligns with a study conducted by Chan *et al*[15] in China, where nearly 90% of patients achieved remission following induction therapy with prednisolone combined with either MMF or CYC. In contrast, the remission rate was relatively higher compared to studies conducted by Prasad *et al*[16] in India, and Rasheed *et al*[17] in Iraq, in which 70% and 53% of patients achieved remission at 6 months, respectively. Moreover, the current finding was relatively lower than a study done by Aliyi *et al*[26] in Ethiopia and George *et al*[28] in India, which reported 92.5% and 94.1% of remission at the end of induction therapy, respectively. The considerable variation in remission rates can be attributed to several factors, including differences in sample size, patient age, baseline renal function, chosen treatment regimens (MMF with prednisolone *vs* CYC alone or AZA alone), remission criteria, racial disparities among the studied population, and variations in disease histopathology. At 5 years of follow-up, 68.11% of patients with PLN in our study achieved remission. Out of these, 45.4% of them had a CR, while 22.7% had a PR. This finding is comparable with a study reported by Prasad *et al*[16] from India in which nearly 69% of patients achieved remission at the last follow-up. The overall remission rate found in this study was lower compared to a previous study conducted in Ethiopia[26], which reported an overall remission (CR plus PR) rate of approximately 86.5%. This disparity is largely attributed to variations in the selection of treatment regimens for induction therapy (CYC with prednisolone or MMF with prednisolone), genetics, socioeconomic status, histological classes (PLN *vs* all classes), and type of regimen selected for maintenance therapy.

Our research identified a notable disparity in renal relapse rates between maintenance treatments, with AZA having a rate of 88.2% and MMF having a rate of 11.76%. These findings are in contrast to the outcomes observed in the MAINTAIN trial[29], which showed no difference in renal relapse rate between these two maintenance regimens. The

MAINTAIN trial has a similar design to our study, in which all the patients received induction with IV CYC only, but only for 3 months with a low dose. This incongruity might be ascribed to the variation in the dose and the duration of pulse CYC.

There are limited data on the rate of ESKD due to the shorter follow-up duration and some studies only covering the induction period. However, one of the major strengths of this study is that it offers valuable insights into ESKD progression over a 5-year follow-up period, with 18.4% of patients progressing to ESKD, higher than the 15% reported by Prasad *et al*[16] from India at 10 years. The higher rate may be attributed to differences in renal dysfunction severity, KRT requirements at presentation, and maintenance therapy regimens as more patients on AZA progressed to ESKD.

We observed a mortality rate of 6.8% at 6 months, increasing to 13.5% at 5 years, higher than previously reported studies[29,30]. Prasad *et al*[16] reported a similar mortality rate (13%) from India but at 10 years. There are multiple factors responsible for this. First, we studied only PLN in which the majority were in histological class IV. Second, 9.2% of patients required KRT on arrival because of late presentation. Thirdly, due to the risk of increased opportunistic infections during the intensive phase, there is a possibility of developing pneumonitis, urinary tract infections, and bloodstream infections with sepsis.

In the current study, renal survival at first-year follow-up was 86.4%. This finding is in keeping with two previous studies[15,26]. But renal survival at 5 years was 68.11%, much lower than that reported by Prasad *et al*[16] and Dhir *et al* [27] for Indian patients (89% and 79%, respectively). A possible explanation for the apparent discrepancy is that induction with a combination of IV CYC and corticosteroids produced similar renal survival at 6 months as induction with MMF and corticosteroids reported in published literature[15,26]. It is a maintenance therapy, whether AZA or MMF, which affects the renal outcomes thereafter, as 70% of our patients were on AZA because of financial constraints.

Without any prospective controlled trials, the management of PLN presents considerable difficulties. Ongoing investigations into new drugs for LN hold promise for more personalized treatments, as improved assessment of disease activity and outcomes, along with an expanded armamentarium, become available[31].

Strengths and limitations of the study

One of the key strengths of this study is that it encompasses one of the largest adult cohorts of biopsy-confirmed PLN from a developing South Asian country. The data are very scarce, and no data on the outcomes of PLN from Pakistan have been published. Additionally, our patients have been monitored for more than 5 years, with individual evaluations of treatment outcomes. Moreover, our study provides data on ESKD and mortality rates at the 5-year mark, which are often absent in many previously published PLN studies. However, this study had several limitations as well. First, being a retrospective study, the absence of certain data may have impacted the final analysis. In addition, the retrospective study design may not fully control all the potential confounding factors. Second, since this study was based on data from a single center, it may not fully represent the entire population of the country, which limits the generalizability of the results. Third, the high cost and inconsistent supply of immunosuppressive medications led to most patients being transitioned from MMF to AZA, especially in the early phase of the study. This affected the universality of the results and hindered the accurate evaluation of the different drugs' efficacy.

CONCLUSION

Our findings indicate that baseline eGFR, the necessity for KRT, and the presence of diffuse proliferative disease at presentation are strong predictors of renal survival. Short-term renal outcomes were good with a combination of IV CYC and corticosteroids-based induction therapy, but 5-year renal outcomes were worse with AZA-based maintenance therapy than with MMF with more ESKD and mortality.

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ORIGINAL ARTICLE

Retrospective Study

Survival and treatment of stage IV renal cell carcinoma in academic *vs* non-academic medical centers

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Abstract

BACKGROUND

Renal cell carcinoma (RCC) is treated with surgical resection as the gold standard, as it is notoriously resistant to systemic therapy. Advancements with targeted therapies contribute to declining mortality, but metastatic RCC (mRCC) survival remains poor. One possible factor is treatment at academic centers, which employ advanced providers and novel therapies. This study compared outcomes of mRCC in patients treated at academic/research facilities compared to those treated at non-academic centers.

AIM

To compare survival outcomes of mRCC and their various etiologies between academic and non-academic centers.

METHODS

The National Cancer Database was used to identify mRCC patients including all histology subtypes and stage IV disease. Descriptive statistics and Kaplan-Meier curves measured survival outcomes for user file facility types sorted into a binary academic/research and non-academic research variable. Multivariate logistic regression and Cox proportional hazard testing generated odds ratio and hazard ratio. Data was analyzed using Statistical Package for the Social Sciences version 29.0 using a significance level of $P < 0.05$.

RESULTS
Overall, academic facility patients experienced greater 5-year and 10-year overall survival than non-academic facility patients. Treatment at non-academic facilities was associated with increased odds of death that persisted even after controlling for age, tumor size, sex, and distance traveled to treatment center. In comparison, non-academic facility patients also experienced greater risk of hazard.

CONCLUSION
Patients with mRCC treated at academic/research facilities experienced increased survival compared to patients treated at non-academic facilities, were more likely to be younger, carry private insurance, and come from a large metropolitan area. They also were significantly more likely to receive surgery and adjuvant immunotherapy.

Key Words: Renal cell carcinoma; Academic; Non-academic; Facility; Center; Type; Survival; Outcome

Core Tip: Treatment of renal cell carcinoma (RCC) has been historically challenging. Our objective is to explore the contextual factors influencing RCC patients and their outcomes, primarily between those receiving care at academic compared to non-academic institutions. Previous studies on other cancers have some but limited insight into the remarkable discrepancy in survival in favor of academic centers. We aim to elucidate these findings for RCC using the National Cancer Database which unprecedentedly now enables analyzing large numbers of patients across long spans of time.

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INTRODUCTION

Renal cell carcinoma (RCC) stands as the most common urogenital cancer[1] and ninth most common overall cancer in the world[2]. The most common subtype is clear cell carcinoma accounting for 75% of all RCCs; followed by papillary carcinoma (15%); chromophobe carcinoma (5%); and a miscellaneous collection of others including MiT family translocations (TFE3 fusion with other genes on chromosome Xp11.2), collecting duct, medullary, and oncocytoma that comprise of the remaining 5% of RCCs[3,4]. Multiple hereditary syndromes have also been found to be associated with RCC, accounting for roughly 4% of all cases of RCC[1,5,6]. The majority of RCC patients at the time of diagnosis possess localized tumors, the definitive treatment of the past for primary neoplasms has been radical and partial nephrectomy, with surgical advances in partial nephrectomy techniques *via* open and robotic approaches enabling greater preservation of renal function[3].

Despite advances in therapeutic approaches, metastatic RCC (mRCC) remains a complicated malignancy to treat, and survival rates remain poor[1]. Widespread mRCC is notoriously resistant to chemoradiotherapy and surgical intervention is associated with high rates of recurrence[1,7]. The introduction of new adjuvant modalities in recent decades that have garnered significant attention from the scientific community and demonstrated promising preliminary improvements to overall survival (OS)[8,9]. A multitude of immune checkpoint inhibitors trials have already been conducted or underway [3,10]. Therefore, advanced knowledge of the ever-changing treatment landscape for mRCC increasingly appears as a necessary prerequisite to obtaining optimal patient outcomes.

In addition to developments in systemic therapy, other variables may be impacting survival in mRCC. One notable variable may be treatment volume and facility type. Prior studies have found that increased treatment volume was associated with improved survival in mRCC, and that academic centers had greater utilization of immunotherapy compared to non-academic facility types. Prior studies on cancers such as non-small cell lung cancer (NSCLC), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma have shown that patients treated at academic centers often achieve superior outcomes compared to those treated at non-academic facilities. These findings have been attributed to a combination of factors, including access to specialized care, clinical trial availability, and multidisciplinary expertise[11-13].

Despite these insights, the disparity in survival and treatment practices between academic and non-academic facilities in mRCC has not been thoroughly investigated. Understanding these differences is essential, as it can inform targeted interventions to bridge gaps in cancer care quality and improve outcomes across diverse healthcare settings. This study aims to address this knowledge gap by examining survival outcomes and treatment patterns for patients with mRCC treated at academic *vs* non-academic centers. By leveraging data from the National Cancer Database (NCDB), this study provided a comprehensive analysis of how facility type influences mRCC survival, treatment modalities, and demographic factors.

MATERIALS AND METHODS

Data source and study population

This study utilized data from the NCDB, a hospital-based registry representing approximately 70% of new cancer diagnoses across the United States. Patients included in this study were patients diagnosed with stage IV RCC (mRCC) between 2004 and 2020. All histologic subtypes of RCC were included; stage IV RCC was classified based on the criteria of the American Joint Commission on Cancer and the corresponding ICD-O-3 code C649. The exclusion criteria were missing survival data, unknown tumor node metastasis (TNM) staging, and T1-3 staging without the presence of metastatic disease.

Facility classification

The Comission on Cancer categorizes cancer programs based on facility type, structure, services, and annual case volumes. Academic/research facilities are characterized by their involvement in medical education across multiple specialties, including internal medicine and general surgery, and handle over 500 new cancer cases annually. National Cancer Institute-designated comprehensive cancer centers are also recognized as "academic/research" facilities due to their comprehensive involvement in research, clinical trials, medical education, and oncologic care.

The participant user file encoded four facility subtypes: (1) Academic/research programs; (2) Community cancer programs; (3) Comprehensive community cancer programs; and (4) Integrated network programs. A binary "academic/research" and "non-academic research" variable was created to serve as the overarching umbrella categories for academic and non-academic facility types. The facility type "academic/research programs" was placed in the "academic/research" variable. The remaining three facility types "community cancer programs", "comprehensive community cancer programs", and "integrated network programs", were grouped into the "non-academic research" variable.

Statistical analysis

Descriptive statistics and Kaplan-Meier curves were used to measure OS between academic and non-academic facility types. Multivariate logistic regression and Cox proportional hazard testing were used to generate odds ratio (OR) (95%CI) and hazard ratio (HR) (95%CI) between academic and non-academic facility types. Demographic, socioeconomic, clinical characteristics, and treatment characteristics were sub-stratified and compared between facility types. Additional values were calculated adjusted for age, sex, and median household income. Data was analyzed using Statistical Package for the Social Sciences version 29.0 and statistical significance was set at 0.05.

RESULTS

OS

Analysis of survival outcomes revealed that patients treated at academic facilities exhibited significantly improved OS compared to those at non-academic centers (Table 1). The median OS for academic institutions was 13.7 months (95%CI: 13.3–14.1), whereas non-academic facilities had a median OS of 8.94 months (95%CI: 8.75–9.13). At the 5-year mark, OS was 17.0% at academic centers and 11.5% at non-academic centers ($P < 0.05$). Similarly, the 10-year OS was 9.2% at academic centers *vs* 5.5% at non-academic facilities ($P < 0.05$). Kaplan-Meier survival curves further illustrated this divergence, with a statistically significant difference in survival between the two facility types (Figure 1).

Demographic, socioeconomic, and clinical characteristics

The demographic and socioeconomic profiles of patients varied notably by facility type. Patients treated at academic centers were generally younger, with a mean age of 63.8 years (SD = 10.9) compared to 66.6 years (SD = 11.4) at non-academic facilities ($P < 0.05$). Geographic and socioeconomic differences were also apparent: Patients treated at academic centers traveled an average of 57.6 miles (SD = 148) for treatment, significantly farther than the 23.8 miles (SD = 86.7) reported for non-academic centers ($P < 0.05$). Academic centers served a higher percentage of privately insured patients (40.7% *vs* 35.9%) and a lower proportion of patients on Medicare (43.4% *vs* 54.5%) ($P < 0.05$). A larger share of patients treated at academic facilities resided in metropolitan areas with populations exceeding 1 million (51.6% *vs* 44.6%) ($P < 0.05$), whereas smaller metropolitan areas contributed more patients to non-academic centers (Table 2). There were significant differences in comorbidity scores between facility types. At academic centers, 71.4% of patients had a Charleson-Deyo comorbidity score of 0, compared to 67.1% at non-academic centers ($P < 0.05$).

Treatment characteristics

Treatment initiation times varied significantly between academic and non-academic centers. Surgical interventions were initiated an average of 43.1 days from diagnosis at academic centers *vs* 37.4 days at non-academic centers ($P < 0.05$) (Table 3). Systemic therapy, including chemotherapy, began an average of 64.5 days after diagnosis at academic centers, compared to 55.8 days at non-academic centers ($P < 0.05$). Radiation therapy and immunotherapy were also delayed at academic centers, with initiation times of 51.9 days and 75.7 days, respectively, compared to 41.9 days and 67.4 days at non-academic centers ($P < 0.05$ for each).

Patients at academic centers were more likely to undergo surgical intervention, including radical nephrectomy (RN) compared to patients at non-academic centers (RN = 47.1% *vs* RN = 27.5%) ($P < 0.05$). Furthermore, academic centers exhibited a greater utilization of adjuvant therapies. Rates of adjuvant chemotherapy, radiation, and combined chemora-

Table 1 5-year and 10-year overall survival

Variable (*n* = 79367)	Academic (*n* = 30780)	Non-academic (*n* = 48587)	*P* value
5-year OS (%)	17.0	11.5	< 0.05
10-year OS (%)	9.20	5.50	< 0.05

OS: Overall survival.

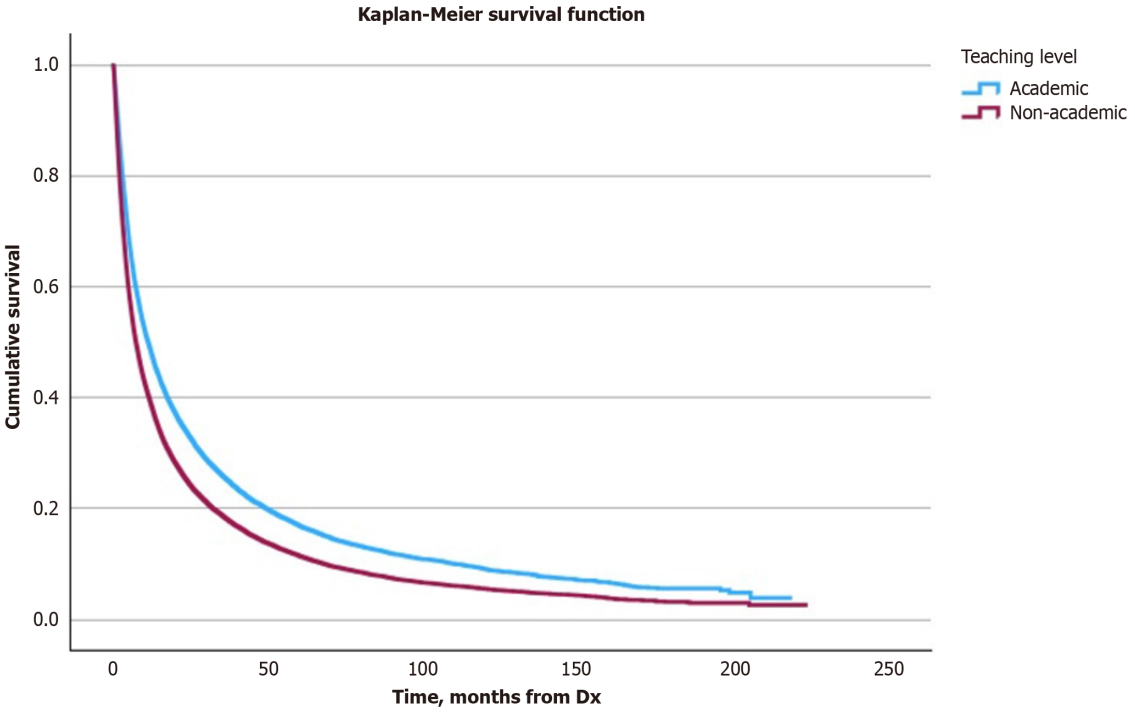

Figure 1 Kaplan-Meier survival outcomes over time of academic *vs* non-academic facility types.

diation were all higher at academic centers (4.4%, 1.3%, and 0.2%) than at non-academic centers (3.7%, 1.1%, and 0.4%) ($P < 0.05$). There also was greater utilization of immunotherapy at academic centers (17.1% *vs* 14.1%) ($P < 0.05$).

Multivariate analysis

Multivariate regression analyses indicated that non-academic facility type was associated with poorer survival outcomes. The Cox proportional hazard model, unadjusted, yielded a HR of 1.27 (95%CI: 1.24-1.29) ($P \leq 0.05$), signifying a 27% higher risk of mortality for patients treated at non-academic centers (Table 4, Figure 2). The unadjusted OR for mortality at non-academic facilities was 1.34 (95%CI: 1.30–1.40) ($P \leq 0.05$). When adjusted for age, tumor size, sex, and travel distance, the OR remained elevated at 1.23 (95%CI: 1.18–1.28) ($P \leq 0.05$).

DISCUSSION

This study provides a comprehensive analysis of survival outcomes and treatment characteristics for patients with mRCC treated at academic and non-academic healthcare facilities using data from the NCDB. Our findings demonstrate that patients treated at academic centers experienced significantly improved OS compared to those at non-academic facilities. These results align with prior studies reporting superior outcomes at academic centers across various cancer types, including NSCLC, lymphoma[11], and multiple myeloma[12-16].

OS between facility types

The primary finding of this study is the substantial survival advantage observed for patients treated at academic centers, with 5-year and 10-year OS rates of 17.0% and 9.2% compared to 11.5% and 5.5% at non-academic centers, respectively. This difference persisted after adjusting for key demographic and clinical covariates such as age, tumor size, sex, and distance traveled. These findings are consistent with prior literature showing that patients treated at academic centers were more likely to receive advanced interventions, including immunotherapy and surgical procedures[17]. Enhanced survival benefits at academic centers have also been observed in early-stage NSCLC, as well as superior surgical quality

Table 2 Demographic, socioeconomic, and clinical characteristics of patients with metastatic renal cell carcinoma, *n* (%)

Variable (*n* = 79367)	Academic facility (*n* = 30780)	Non-academic facility (*n* = 48587)	*P* value
Age [mean (SD)]	63.8 (10.9)	66.6 (11.4)	< 0.05
Distance travelled [mean (SD)]	57.6 (136)	23.8 (86.7)	< 0.05
Sex			0.511
Male	21428 (69.6)	32637 (67.2)	
Female	9352 (30.4)	15950 (32.8)	
Insurance status			< 0.05
Race			< 0.05
White	42600 (88.4)	25591 (84.1)	
Black	4160 (8.6)	3473 (11.4)	
Other	1441 (3.0)	1363 (4.5)	
Race-missing data	739		
Private insurance	11954 (40.7)	16790 (35.9)	
Medicaid	2747 (9.4)	3120 (6.7)	
Medicare	12744 (43.4)	25470 (54.5)	
Other government	482 (1.6)	707 (1.5)	
Insurance Status unknown	1418 (4.8)	653 (1.4)	
Income class			< 0.05
< $38000	3666 (11.9)	5495 (11.3)	
$38000-$47999	5422 (17.6)	7993 (16.5)	
$48000-$62999	6032 (19.6)	10782 (22.2)	
> $63000	9327 (30.3)	1317 (27.1)	
Urban/Rural			< 0.05
Metro area greater than 1 million people	15886 (51.6)	21670 (44.6)	
Metro area 250000–1 million	5856 (19.0)	10980 (22.6)	
Metro area < 250000	9038 (29.4)	15937 (32.8)	
Tumor size [mean (SD)]	481 (450)	469 (453)	< 0.05
Facility location			< 0.05
New England	2322 (4.8)	1496 (4.9)	
Middle Atlantic	4540 (9.3)	6164 (20.0)	
South Atlantic	10448 (21.5)	5796 (18.8)	
East North Central	8959 (18.4)	4851 (15.8)	
East South Central	3883 (8.0)	1758 (9.6)	
West North Central	4211 (8.7)	2955 (12.3)	
West South Central	5186 (10.7)	3793 (12.3)	
Mountain	2189 (5.8)	859 (2.8)	
Pacific	6219 (12.8)	3108 (10.1)	
Regional lymph nodes positive	77.6 (39.4)	85.7 (32.2)	< 0.05
Charleson-deyo score			< 0.05
0	22077 (71.4)	32286 (66.4)	
1	5638 (18.3)	10001 (20.6)	
2	1784 (5.8)	3715 (7.6)	

3	1281 (4.2)	2585 (5.3)

Table 3 Treatment characteristics of patients with metastatic renal cell carcinoma, *n* (%)

Variable (*n* = 1068)	Academic (*n* = 30780)	Non-academic (*n* = 48587)	*P* value
Definitive surgical procedure, days from Dx [mean (SD)]	43.1 (63.7)	37.5 (61.5)	< 0.05
Systemic therapy initiated, days from Dx [mean (SD)]	64.5 (57.1)	55.8 (54.2)	< 0.05
Chemotherapy initiated, days from Dx [mean (SD)]	64.9 (61.3)	56.2 (54.9)	< 0.05
Radiation therapy initiated, days from Dx [mean (SD)]	56.1 (76.8)	45.8 (61.6)	< 0.05
Immunotherapy initiated, days from Dx [mean (SD)]	75.6 (65.9)	67.5 (72.9)	< 0.05
Surgical inpatient stay [mean (SD)]	5.64 (7.46)	5.40 (6.92)	0.006
Surgery of primary site			< 0.05
Subtotal nephrectomy	624 (2.0)	612 (1.3)	
Complete nephrectomy	876 (2.8)	1417 (2.9)	
Radical nephrectomy	11,419 (37.1)	13382 (27.5)	
Surgery, other	1,015 (3.3)	1052 (2.2)	
Surgery of primary site not performed	16,846 (54.7)	32124 (66.1)	
Adjuvant therapy			< 0.05
Adjuvant chemoradiation	65 (0.2)	190 (0.4)	
Adjuvant radiation	412 (1.3)	514 (1.1)	
Adjuvant chemotherapy	1350 (4.4)	1779 (3.7)	
No adjuvant therapy	28953 (94.1)	46104 (94.9)	
Immunotherapy			< 0.05
Received immunotherapy	5264 (17.1)	6864 (14.1)	
Did not receive immunotherapy	25132 (81.7)	41075 (84.5)	
Unknown if received immunotherapy	384 (1.2)	648 (1.3)	

Table 4 Multivariate regression models for association of non-academic facility type with poor survival outcomes

Variables	Odds ratio/HR	95%CI	*P* value
Crude model (unadjusted)	1.34	1.30-1.40	< 0.05
Model adjusted for age, tumor size, sex, and distance travelled	1.23	1.18-1.28	< 0.05
Cox proportional model for HR (unadjusted)	1.27	1.24-1.29	< 0.05

Reference predictor: Academic facility type. Reference outcome: Living status. HR: Hazard ratio.

with respect to 30-day and 90-day postoperative outcomes and median lymph nodes removed[11,14,15]. Similar trends have been noted for other malignancies, such DLBCL and multiple myeloma where patients at academic centers demonstrated significantly improved survival outcomes. These results were especially profound for high-risk DLBCL patients at academic centers, who demonstrated more than twice the median survival than those at non-academic centers [12,13]. Vardell *et al*[13] proposed that this discrepancy may be due to greater funding, easier access to clinical trials and stem cell transplants, and large integrated support care structures at academic institutions that simply do not exist or, at the very least, are difficult to acquire at non-academic centers. Other studies have suggested that academic facilities generally see greater hospital volume than non-academic facilities and are equipped with specialized multidisciplinary treatment facilities, equipment, and infrastructure, all of which lend themselves to greater breadth of specialized knowledge and ability to handle complications from treatment[14,15].

Demographic differences between facility types

Patients with mRCC treated at academic facilities were younger, carry private insurance, and come from a higher median

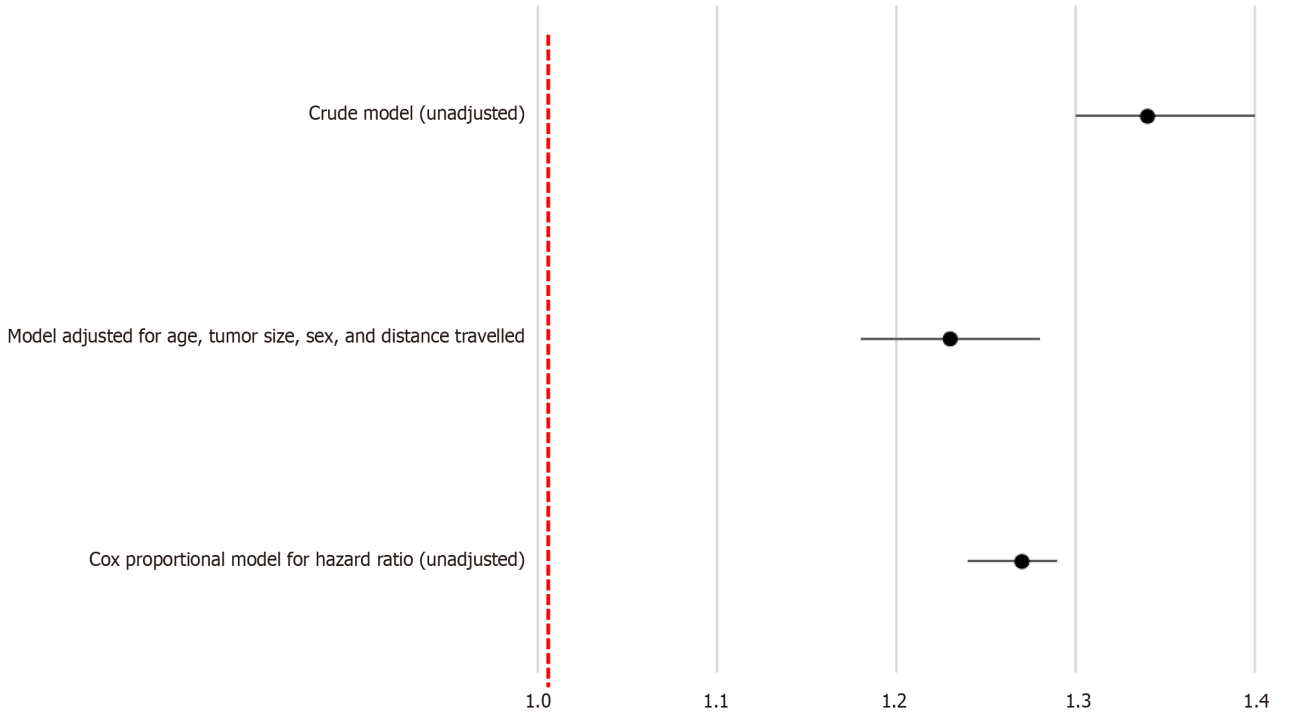

Figure 2 Odds ratio/hazard ratio of multivariate regression models for association of non-academic facility type with poor survival outcomes.

income quartile[11], which is consistent with the results of prior studies[12-16]. One notable finding was that patients at academic centers traveled significantly greater distance for their mRCC treatment. Given the complex nature of the disease, however, mRCC may warrant a longer journey for its patients to receive tertiary care treatment (*i.e.* at academic centers) in comparison to other cancers, however, this distance travelled may represent a barrier to care for some patients. Socioeconomic and demographic factors likely influence patients' decision-making in the location at which they seek medical care. These findings suggest that this decision making process may directly or indirectly be associated with prognostic outcomes in mRCC.

Treatment characteristics

Our analysis identified significant differences in the timing and intensity of treatments between facility types. Patients at academic centers experienced longer intervals between diagnosis and initiation of various treatments, including surgery, systemic therapy, and immunotherapy. These delays may reflect the additional time required for comprehensive evaluations, consultations with specialists, and coordination of care in academic settings, where multidisciplinary approaches are often emphasized[13-15]. Coordination of care of a single patient already involves multiple different types of professional healthcare providers, which at academic centers is even more complicated by the accommodation of those still in various stages of training, including medical students and resident physicians[16]. The continuum of patient needs is dynamic and contains "transition points" at which multidisciplinary care team members must meet and deliberate priorities of care and adjust interventions and team compositions accordingly, all of which involves the input from a multitude of different professionals[18]. For all modes of mRCC treatment in this study, the average treatment delay at academic centers compared to non-academic centers was no longer than ten days. While statistically significant, this delay in treatment is fairly short and is unlikely to impact prognosis or mortality for patients. A treatment delay of up to 6.3 weeks from the diagnosis of RCC was found to not significantly affect outcomes and survival[19,20]. Another study found that a minimum of a four week delay of cancer treatment is associated with increased mortality across surgical, systemic treatment, and radiotherapy indications for seven different cancers[21].

Implications for clinical practice

These results suggest that adherence to evidence-based management guidelines remains critical for a number of aggressive malignancies like mRCC, where robust prognostic and therapeutic strategies are paramount for optimizing outcomes[22,23]. Potential improvement of the prognosis in mRCC largely depends on robust detection and utilization of targeted treatment modalities. Within the detection the TNM classification system remains the gold standard, which simultaneously accounts for stage, grade, tumor subtype, clinical features, and performance[5,24,25]. Prognostic scoring of mRCC uses a modified Glasgow prognostic score to stratify the risk of RCC[26]. Molecular markers such as WDR72 have garnered more attention in recent years, with an increasing number of novel markers associated with RCC being found[27]. However, in addition to the complicated challenge of obtaining and maintaining samples, currently they are only used occasionally as an adjunct to improve the accuracy of existing prognostic models due to their poor external validity and impractical implementation because of tumor heterogeneity[28,29]. Treatment for mRCC has rapidly

evolved, beginning when the anti-angiogensis agent Vascular endothelial growth factor receptor-tyrosine kinase inhibitor (TKI) sunitinib demonstrated superiority compared to interferon-alpha (IFN-α). Currently, clear cell mRCC with intermediate risk is treated by sunitinib/pazopanib/bevacizumab and IFN-a (1st line) or sorafenib/axitinib (2nd line)[1,5,30]. Patients with clear cell mRCC with intermediate risk who failed TKI receive sorafenib/everolimus/temsirolimus/axitinib. Poor-risk clear cell mRCC and non-clear cell mRCC patients receive temsirolimus. Radiotherapy is an adjunct modality used but to limited effect due to the apparent radio-resistant nature of RCC neoplasms[1]. As alluded to before, a preeminent aspect of current challenges in pharmacological development is the significant discontinuation rates of patients in previous drug trials due to debilitating adverse effects[31]. A large portion of the *modus operandi* in contemporary treatment with adjuvant therapy was and still is preemptive recurrence risk stratification such that as few low-risk patients may need to undergo adjuvant therapy, and thus be exposed to their potential side effects, as possible. Considering mRCC is a clinically challenging malignancy for providers to treat and the limited detection and treatment options available, it is paramount that physicians adhere to existing guidelines to optimize survival for as long as possible.

Bridging the gap between facility types

Given the relative rarity of academic centers, it is most likely a practical infeasibility to recommend academic center healthcare to all patients. Perhaps a solution to bridge the gap between academic and non-academic medical centers could be involvement in research pertaining to RCC. Physicians at academic centers could begin to incorporate community physicians in the research that is conducted at large academic centers, to encourage active involvement in the latest technologies and information[32]. This method also bears the potential to expand clinical trials at academic centers to broaden the number and diversity of the participants. In addition, academic centers often host didactic sessions, providing attendees insight into current literature[32]. Incorporating community-based physicians into this continuing educational model could narrow the gap in outcomes, by sharing resources that the community-based physicians would otherwise not have access to. Strengthening connections between academic and non-academic providers would provide a net positive for the patients affected by mRCC and could improve outcomes for those affected by this disease.

Limitations

While this study provides valuable insights, several limitations must be acknowledged. First, as a retrospective analysis of NCDB data, it is subject to inherent biases, including selection bias and uncontrolled confounding. Patients at academic centers may differ systematically from those at non-academic facilities in ways not fully captured by the available covariates. Second, the use of registry data introduces potential inaccuracies, as coding errors and incomplete documentation in the NCDB could influence the findings. Finally, unmeasured variables such as molecular biomarkers, detailed treatment adherence, and socioeconomic support systems may further confound the observed relationships in ways beyond the currently available information encoded within the NCDB database.

CONCLUSION

Patients treated at academic institutions experienced superior survival outcomes compared to their counterparts at non-academic facilities. Moreover, they were younger ages, carried private insurance, and resided in larger metropolitan areas. Disparities can potentially be reduced by integrating community healthcare services in research and education alongside academic centers.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Improving outcomes in foley catheterization: A retrospective review with a proposed protocol

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Abstract

BACKGROUND

Urologists are commonly consulted regarding difficult and traumatic urethral catheterizations. Complications surrounding Foley catheterizations represent a significant burden to the healthcare system.

AIM

To assess the demographic and patient characteristics surrounding urological consultation for difficult and traumatic Foley catheterizations at our institution across multiple hospitals.

METHODS

This is a single-institution, multi-hospital, 263 patient, retrospective chart review from Jan 2020–December 2023.

RESULTS

The majority of consultations (80.2%) did not require heroic measures by the urology service. A Foley catheter placement was determined not difficult in the majority 191 (72.6%) of patients. Sub-group analysis of "difficult by urology" *vs* "not difficult by urology", showed a significant difference between those with zero attempts, one attempt, and greater than one attempts (P = 0.004). Those patients specifically with greater than one attempts were more likely to be seen as a difficult insertion by urology assessment (60.6%) compared to not difficult (38.6%). Likewise, those patients with a history of difficult urethral catheter (DUC)/traumatic urethral catheterization (TUC) (25.8%) were more likely to be difficult compared to those without a history of DUC/TUC (14.2%) (P = 0.038).

CONCLUSION

The study found that majority of consultations received did not require heroic measures by the urology service to place a catheter. Patients who had a history of DUC/TUC and those who had greater than one catheter attempts were statist-

ically more likely to be a DUC based on urology assessment. At our institution we hope to propose a protocol in which nursing staff and non-urologic clinicians will utilize a troubleshooting checklist and an algorithm when difficult or traumatic urethral catheters are encountered in order to improve patient care and decrease healthcare costs. For example, this protocol would ideally address complications of multiple catheter attempts such as urethral trauma, development of urethral strictures, and infection risk. Additionally, future trainings and availability of additional resources will be provided and assessed with a goal of reducing healthcare cost surrounding these complications.

Key Words: Patient care; Education; Traumatic catheter; Difficult catheter; Foley catheter; Urology

Core Tip: We performed a single institution, retrospective review of 263 consultations for "difficult urethral catheter" or "traumatic urethral catheter". The study found that of total consultations, 80.2% did not require heroic measures. A Foley catheter placement was determined not difficult in 73% of patients. Patients who had a history of difficult or traumatic catheter and those who had greater than one catheter attempts were statistically more likely to be a difficult urethral catheter. At our institution we hope to propose a protocol in which nursing staff will utilize a troubleshooting checklist and an algorithm when difficult urinary catheter or traumatic catheters are encountered to promote improved patient care.

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INTRODUCTION

Urologists are commonly consulted regarding difficult and traumatic urethral catheterizations (TUC). An anatomic or structural abnormality is usually the culprit when placing a catheter into the bladder causing a difficult urethral catheter (DUC). Bleeding and/or injury to the urethra from TUC due to multiple failed catheter attempts can follow. Approximately 10%-25% of hospitalized patients undergo urethral catheterization[1]. A DUC may be due to anatomic challenges in male patients including: Urethral strictures, phimosis, or false passages[2]. In females, challenges exist in the postmenopausal setting due to intravaginal retraction of the urethral meatus[2]. Traumatic insertions occur after repeated failed attempts to cannulate the urethra and may lead to acute urinary retention, urosepsis, bleeding, acute kidney injury, and urethral strictures[3]. The incidence of TUC in hospitalized patient is approximately 13.4 per 1000 catheter attempts [3]. Complications of traumatic catheter insertion can include the development of urethral strictures. Prior studies quote a majority (78%) of patients developing urethral strictures after being seen for a TUC[3]. The associated healthcare costs of managing iatrogenic urethral injuries may translate to $371790 per patient[4]. These findings emphasize the need for developing solutions to decrease the complications surrounding catheterizations.

Prior to urology consultation, studies report an average of 1.6 catheter attempts by previous providers[5]. DUC is treated and managed based on the anatomic etiology. Most catheters can be successfully inserted using the appropriate exposure or with the use of different tip catheters (*e.g.* Coude catheter)[6]. In rare cases, the need of surgical placement of a urethral catheter *via* cystoscopy or insertion of a suprapubic tube can be completed by a trained urologist[6]. Approximately 41% of consultations received for difficult Foley placement do not require special interventions or maneuvers[7]. Protocols exist that can help health care professionals in different settings such as the emergency room or medical floor to improve success in catheter placement and better techniques in complex patients[8]. However, there is a lack of data surrounding the study of difficult and TUC and the requirement of consultation. Implementation of nursing protocols surrounding traumatic catheters may lead to decreased incidence of urethral injury[4]. Traumatic catheterization and inability to place a urethral catheter among nursing staff is common, with a need and desire for a protocol and education regarding catheterizations[9]. Prior studies highlight the success of designed protocols that combine an education program, catheter algorithm, and skilled nursing catheter nursing team and showed a reduction the frequency of catheter-associated trauma and procedures[10]. Although, there still remains a need in the literature for further studies regarding prevention, education, and awareness surrounding catheter management[7].

This study aimed to assess the demographic and patient characteristics surrounding urological consultation for difficult and traumatic Foley catheterizations at our institution across multiple hospitals. Future trainings and availability of additional resources at our institution will be added and assessed with a goal of reducing and preventing complications associated with these consultations. This will be accomplished by providing examples of algorithms for female (Figure 1) and male (Figure 2) difficult catheter insertions to the nursing staff at our institutions across different departments.

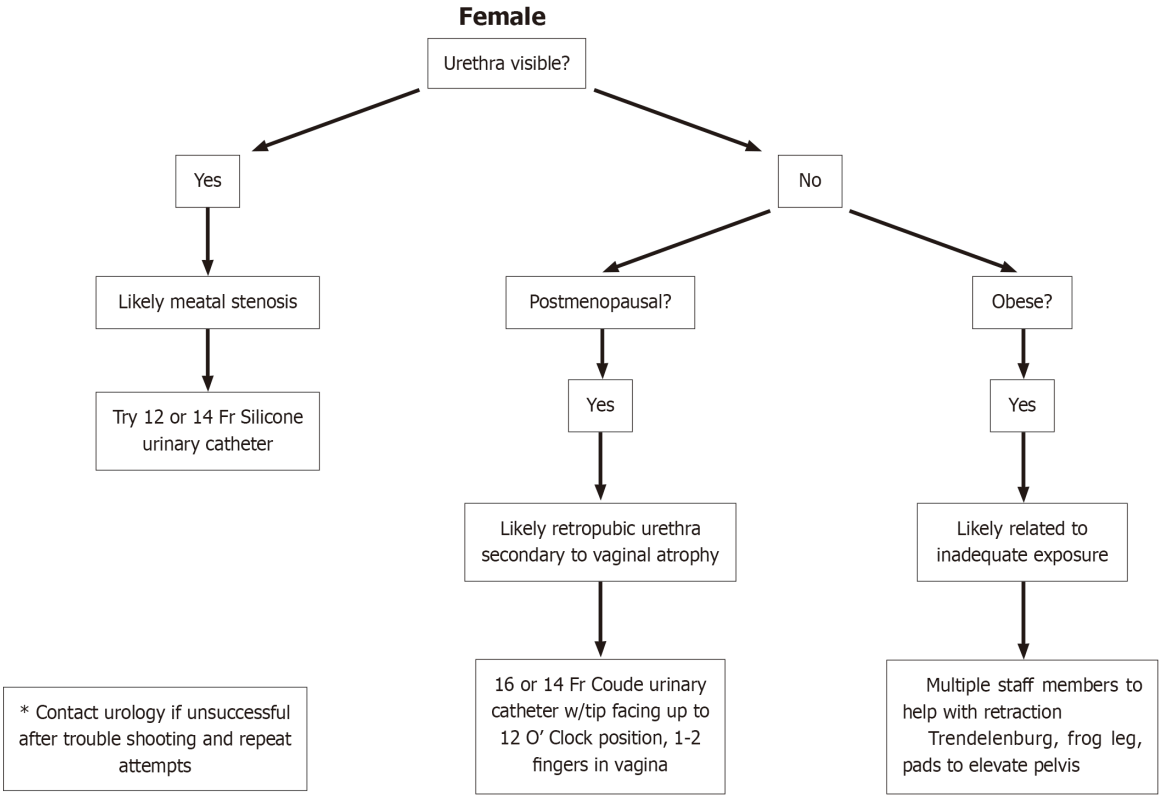

Figure 1 Algoithm provided to nursing staff for troubleshooting difficult urethral catheter in female patients.

MATERIALS AND METHODS

After institutional review board approval was given, retrospective chart review was performed over a three years period including 263 patients. Inclusion variables including either "difficult urethral catheter" or "traumatic urethral catheter" were queried. Patients that were included are those who were seen and consulted at our institutions during the data collection period for either difficult or traumatic catheterization as the consulting diagnosis. Included patients had a completed consultation note documenting the nature of the consult and the interventions or steps completed by the on call urologist. Additional information was obtained from the general information of each patient's medical record. Descriptive variables of the patients were collected including age, biological sex, body mass index (BMI), and race by review of background information for those meeting inclusion criteria. Reason for consultation was collected and reported as either DUC, TUC, or both, based on the consultation diagnosis or order. DUC was defined as a consultation to the urology service for placement of Foley catheter where a nursing or physician noted difficulty on catheter insertion. TUC was defined as either gross hematuria or a malpositioned catheter. This information was detailed in the "history" portion of the consultation note during the history taking by the urologist. Data was collected including whether the urology team considered the foley catheter insertion difficult or if procedural techniques were needed. Difficulty was overall defined and determined by the need of bedside or operating room procedures for catheter insertion, or other means requiring urology assessment that a nursing staff or non-urological physician alike could not otherwise accomplish to insert the catheter. Information regarding operating or procedural intervention was collected from the "impression" and "plan" sections of the consultation note. Insertion of routine Coude catheter or 3-way port catheters were not considered difficult unless the consulting urologist required additional materials or procedural techniques. The type of catheter inserted by urology was also reported. The type of catheter was reported in either the "physical exam" or the "plan" portion of the consultation note.

Quality metrics were collected and reported as length of stay, development of catheter-associated urinary tract infection (CAUTI), and amount of prior nursing or non-urological physician attempts at catheter insertion prior to consultation. The length of stay was recorded by reviewing the current admission and discharge date of the patient based on when the consult was placed. CAUTI was recorded by reviewing the presence of positive urine cultures obtained from the patient during the hospitalization after the catheter was placed by the consulting urologist. Amount of catheter attempts by nursing were collected using the "history" portion of the consultation note. We collected patient data on history of prior difficult or traumatic catheter insertions that required a urology consult previously by reviewing the "history" portion of the consultation note or by reviewing prior consultation notes for the same patient by the urology service on a previous admission.

The responses were collected and reported using mean, medians, and standard deviations, where applicable. Statistical analyses were reported using SPSS software including Student's t test, Fisher exact probability test, and χ^2 analyses.

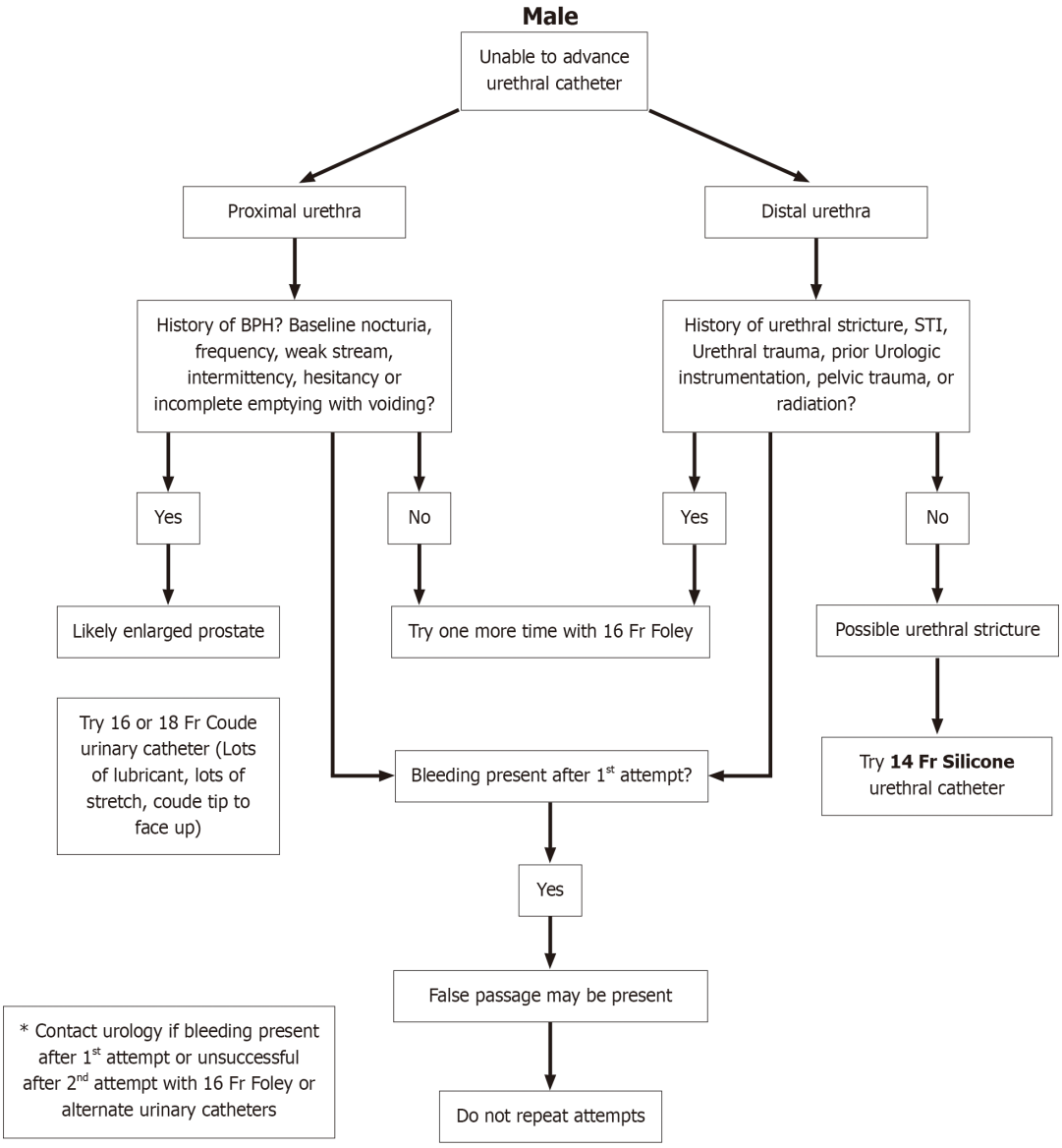

Figure 2 Algoithm provided to nursing staff for troubleshooting difficult urethral catheter in male patients.

RESULTS

A total of 263 consultations were reviewed during the study period of three years across six hospitals at a single institution. The average age of the patient population was 65.6 years, ranging from 18-99 years of age. The mean BMI of the patients is 27.9, ranging from 13-78. On average, 237 (90.1%) consultations were male and 26 (9.9%) were female patients. The background race of consultations was, on average, 147 (55.9%) African American, with an additional 75 (28.5%) being white, 9 (3.4%) being multiple races, 3 (1.1%) Cuban, 1 (0.4%) Hispanic, and 28 (10.6%) without documentation of race (Table 1).

Overall, 138 (52.2%) consultations were for DUC, 43 (16.3%) for TUC, and 82 (31.2%) had both components of DUC and TUC (Figure 3). Of the total consultations, 211 (80.2%) did not require surgical intervention by the urology service with 50 (19.2%) requiring urologic intervention. A Foley catheter placement was determined difficult by the urology service in 66 (25.1%) of consultations and not difficult in the majority, 191 (72.6%) of patients, with 6 (2.3%) consultations not having proper documentation or assessment of catheter difficulty by urology. The type of Foley used most commonly by the treating urologist was 16 French (Fr) straight Foley (26.6%), followed by a 18 Fr Coude (15.2%), 20 Fr Coude (9.9%), 16 Fr Council tip (5.7%), 18 Fr Council (4.2%), 18 Fr straight Foley (4.2%), and 22 Fr 3-way catheter (4.2%), with 8.0% of catheter type not documented (Figure 4). A CAUTI was reported in 35 (13.3%) of patients and no evidence of CAUTI in 228 (86.7%) of patients.

Total catheter attempts before urology evaluation were documented as greater than one attempt in 114 (43.3%), one attempt in 113 (43.0%), and zero attempts in 33 (12.5%) patients, with three (1.1%) without documentation of catheter attempt number. The average length of stay for patients consulted was 15.6 days, median length of stay being 11.0 days, and ranged from 0-123 days. Prior history of DUC or TUC was documented for 45 (17.1%) of patients consulted and no prior history in 217 (82.5%) of patients, and one (0.4%) patient without documentation provided.

Table 1 Baseline demographics of patient cohort collected during the study period for patients consulted for difficult or traumatic catheterizations, *n* (%)

Total (*n* = 263)	Average	Range
Age (years)	65.6	18-99
BMI	27.9	13-78
Race		
AA	147 (55.9)	
Cuban	3 (1.1)	
Hispanic	1 (0.4)	
White	75 (28.5)	
Multiple	9 (3.4)	
Unknown	28 (10.6)	
Sex		
Male	237 (90.1)	
Female	26 (9.9)	

AA: African American; BMI: Body mass index.

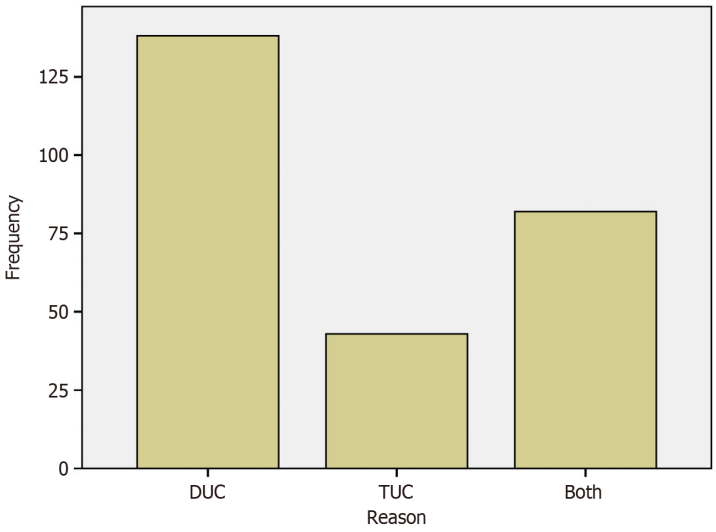

Figure 3 Frequency of consultation diagnosis placed to the urology service for foley catheter insertion listed as either difficult urethral catheter, traumatic urethral catheters, or both.

A sub-group analysis was obtained comparing demographic and clinical differences between the cohort of patients deemed "difficult by urology" *vs* "not difficult by urology" after catheter insertion and evaluation. There were no statistically significant differences between race, sex, and CAUTI between the two groups. When comparing the two groups with regards to catheter attempts, there was a significant difference between those with zero attempts, one attempt, and greater than one attempts (P = 0.004). Those patients specifically with greater than one attempts were more likely to be seen as a difficult insertion by urology assessment (60.6%) compared to not difficult (38.6%) across the other groups (Table 2). This translates to the cohort of patients who had greater than one catheter attempts were statistically more likely to be a DUC on urology assessment. This may be due to trauma to the urethra from multiple failed attempts that require better visualization *via* cystoscopy or from a prior urological history of the patient that requires urological assistance to place the catheter. In this study we did not consider prior urological history as a factor to study among patients included, which would be an additional interesting variable to consider in a future study. Likewise, those patients with a history of DUC/TUC (25.8%) were more likely to be difficult compared to those without a history of DUC/TUC (14.2%) after urology assessment (P = 0.038) (Table 2). Therefore, patients who had a history of DUC/TUC were more likely to be report as a DUC by the consulted urologist based on this sub-group analysis and statistically analysis. This is likely due to an underlying urological history requiring urological assistance to place the catheter however this is a factor that was not evaluated at this time.

Table 2 Sub-group analysis comparing demographic and clinical differences between the cohort of patients deemed "difficult by urology" *vs* "not difficult by urology" after catheter insertion and evaluation, *n* (%)

	Difficult by urology	Not difficult by urology	Unknown	*P* value
Total	66 (25.1)	191 (72.6)	6 (2.3)	
Race			33 (12.5)	0.506
AA	34 (58.6)	108 (62.8)		
Cuban	1 (1.7)	2 (1.2)		
Hispanic	1 (1.7)	0 (0)		
White	20 (34.5)	55 (32)		
Multiple	2 (3.4)	7 (4.1)		
Sex			6 (2.3)	0.806
Female	5 (7.6)	19 (9.9)		
Male	61 (92.4)	172 (90.1)		
CAUTI				0.836
Yes	8 (12.1)	27 (14.1)	6 (2.3)	
No	58 (87.9)	164 (85.9)		
Catheter attempt			9 (3.4)	0.004
> 1	40 (60.6)	72 (38.6)		
1	18 (27.3)	92 (48.9)		
0	8 (12.1)	24 (12.8)		
History of DUC/TUC			7 (2.7)	0.038
Yes	17 (25.8)	27 (14.2)		
No	49 (74.2)	163 (85.8)		

AA: African American; CAUTI: Catheter associated urinary tract infection; DUC: Difficult urethral catheter; TUC: Traumatic urethral catheter.

DISCUSSION

This study was a single institution, retrospective review of 263 consultations placed to the urology service across several hospitals for either "difficult urethral catheter" or "traumatic urethral catheter." The study found the patient population had an average age of 65, mostly male (90%), African American (55.9%), and an average BMI of 27.9. Of the total consultations, 211 (80.2%) did not require surgical intervention by the urology service. A Foley catheter placement was determined not difficult in the majority 191 (72.6%) of patients. Total catheter attempts before urology evaluation were documented as greater than one attempt in 114 (43.3%), one attempt in 113 (43.0%), and zero attempts in 33 (12.5%) patients. Prior history of DUC or TUC was documented for 45 (17.1%) of patients consulted and no prior history in 217 (82.5%) of patients. Those patients specifically with greater than one attempt were more likely to be seen as a difficult insertion compared to not difficult across the other groups (P = 0.004). Likewise, those patients with a history of DUC/TUC were more likely than those without a history of DUC/TUC to be assessed by the urology team as difficult (P = 0.038). We found that traumatic catheterization and inability to place a urethral catheter among nursing staff is common, with a need and desire for a protocol and education regarding catheterizations[9].

Bacsu *et al*[7] reported on a cohort of 81 patients assessed for DUC requiring urological consultation. Forty-one percent of consultations were classified as inappropriate based on successful placement of standard or Coude catheter by a urologist. In our study, 80.2% of DUC or TUC consultations did not require heroic measures by the urology service. Likewise, 73% of consultations for DUC or TUC were not difficult by the urology service assessment. At our institution we found that most catheter insertions could be performed without urological assistance. This may be due to a lack of education or improper technique with catheter placement in the consulting nurses or physicians, placing a need for further educational sessions surrounding routine catheter placement. If catheters can be successfully placed by the appropriate nurse or provider prior to urology consult this would save the patient multiple catheter attempts as well as decrease in healthcare costs as a result of trauma or potential complications[11]. Similar findings were addressed by Liu *et al*[12], who studied 81 consults at their tertiary care center. In 70% of cases, successful placement was achieved by the urology resident. However, 20% of patients required cystoscopy manipulation and 9% required suprapubic tube placement. Catheterization was achieved without adjunct procedures in the majority of consults[12]. These results support a treatment strategy in which all patients without a prior history of lower urinary tract pathology should

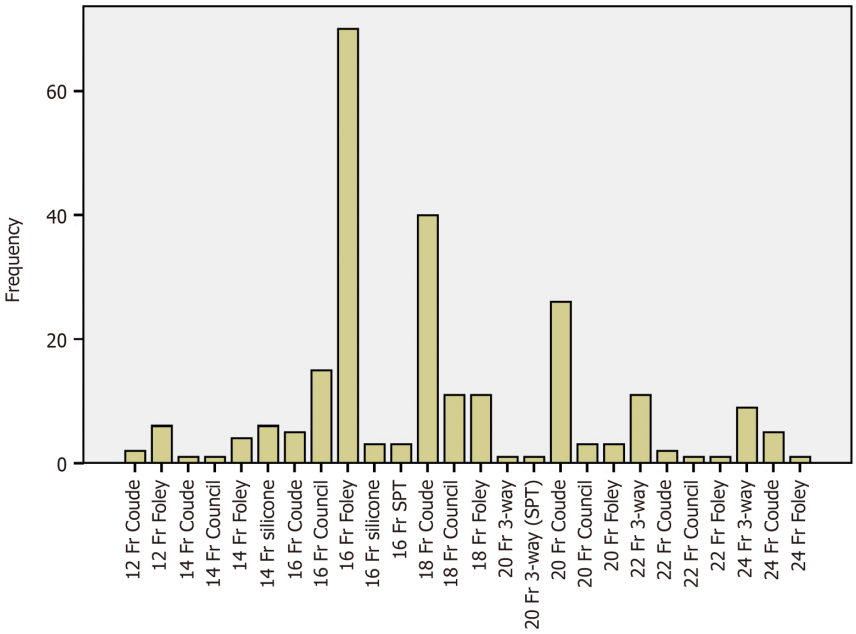

Figure 4 Frequency of common foley catheter types used by the urology service during treatment of difficult or traumatic catheter consultation. SPT: Suprapubic tube.

undergo an initial placement attempt by the primary team or nurses prior to urology consult and encourage continued education by the nursing staff[12].

Additional findings of Bacsu *et al*[7] showed 17% of patients had a history of previous DUC and 65% had a previous urologic history. In our study, a prior history of DUC or TUC was documented for 17% of patients consulted. This value is similar between our studies however we did not consider prior urological history, which would be an additional interesting variable to consider in the future. Patients who had a history of DUC/TUC were more likely to be a DUC based on our sub-group analysis. This is likely due to underlying urological history requiring urological assistance to place the catheter. Additionally, a consultation to urology would be more likely in those with a prior urological history.

Prior studies quote that a majority (90%) of cases have an initial attempt at catheter placement prior to urology consult, with nurses being the most common health care workers to attempt insertion of the catheter[7]. In this study, greater than one catheter attempts were seen in 43% of patients and one attempt in 43% of patients, prior to urology assessment. Prior to urology consultation, studies report an average of 1.6 catheter attempts by previous providers.[5] Interestingly, the zero attempts category in this study yielded a larger number of cases than expected. Prior studies show 6% of consultations are made in which not a single healthcare provider even attempted catheter placement[7]. Approximately 12.5% of patients were noted to have no attempt of catheter placement prior to urology consultation, in this study. This may be due to providers noticing a history of urological consultation and placing a consult proactively, which may be warranted. However, urological consultations may be placed without proper need or before attempts were made. Patients who had greater than one catheter attempts were statistically more likely to be a DUC on urology assessment, based on our sub-group analysis. As previously mentioned, this may be due to trauma to the urethra from multiple failed attempts that require better visualization *via* cystoscopy due to bleeding or from a prior urological history of the patient that requires urological assistance to place the catheter. Placement of a Foley catheter is a common procedure perform by nursing staff and physicians. Nurses and providers should be educated and equipped enough to otherwise place a non-difficult catheter. The increase in healthcare cost and consultation burden would likely increase if urology consults are placed out of ease without the need of a urologic practitioner[4,13].

Patient morbidity and healthcare costs regarding traumatic and difficult catheterization is significant. The nursing staff are usually the first to evaluate and attempt placement of the urethral catheters, making discussion regarding education and protocols important, especially among nursing staff. Prior studies by Laborde *et al*[14] have examined nurse driven Foley catheter protocols and have shown a decrease in catheter-associated trauma after implementation. Likewise, other studies report the need for further improvements in catheter training protocols to avoid iatrogenic complications due to the burden of patient morbidity and health care costs associated with urethral catheter injuries[15]. Some solutions exist and are currently being studied in the literature, such as those proposed by Hackett *et al*[16], suggesting implementation of a rapid response nurse driven training and proficiency programs to assist with decreasing Foley catheter complications. At our institution we hope to propose a protocol in which nursing staff and non-urologic clinicians will utilize a troubleshooting checklist when difficult urinary catheter or traumatic catheters are encountered. Prospectively, traumatic or DUC consults will be tracked at our hospitals before initiating protocol. A newly designed protocol will then be implemented at these hospitals to evaluate for reduction in DUC.

A limitation to this study is the retrospective nature of the data collection. Consultation documentation and assessment of difficulty differed on the chart reviewed depending on which resident or attending received the consultation, potentially leading to an observer bias. In future studies this could be more generalizable if all consultations were

assessed by the same provider to help with similar assessments of difficulty, however this may limit patient case and consultation volume. Likewise, we would have preferred to have additional information on catheter trouble shooting during urological consultation. For example, we were not able to accurately assess the stepwise attempts of the difficult catheter insertion by the urologist consulted (*i.e.* if multiple catheters were tried before successful insertion) based on documentation limitations. Inclusion of the reason or indication for catheter insertion was not included in this study but would be an interesting topic to include in future projects. Lack of adjusting for confounding variables is an additional concern with the retrospective nature of the study. As this study did not include the topics of prior history, patient comorbidities, prior urological surgery, and other factors alike, the generalizability of the study is limited. Likewise, we would have, in hindsight, tried to limit confounding factors by assessing more of the patient's prior urological history and compared this across the subgroups that were difficult *vs* not difficult based on urological assessment. These factors should be studied in future projects as prior urological history is an important factor in troubleshooting difficult Foley insertion when patients present to the hospital. Another limitation that may limit generalizability is the definition of a difficult Foley catheter. For this study, the insertion of a Coude catheter was not defined as difficult. Unless the assessment by urology specified the need for cystoscope or guidewire use for insertion, it was our decision and practice that nursing or non-urology staff can and should learn to place a Coude catheter without the need for consultation. Likewise, the emergency room staff at our institution routinely places 3-way hematuria catheters before consultation to urology therefore those consultations may be deemed not difficult if the catheter placement was without further need for surgical assistance. Our study did include a large volume of patients and provides statistically and clinically significant findings that are novel to medical practice and literature. A future prospective study surrounding difficult and traumatic catheters at our institution after implementation of protocol and trainings would help with generalizing these findings.

CONCLUSION

We performed a single institution, retrospective review of 263 consultations placed to the urology service for either "difficult urethral catheter" or "traumatic urethral catheter". The study found that of the total consultations, 80.2% did not require heroic measures by the urology service. A Foley catheter placement was determined not difficult in 73% of patients. Patients who had a history of DUC/TUC and those who had greater than one catheter attempts were statistically more likely to be a DUC based on urology assessment. At our institution we hope to propose a protocol in which nursing staff and non-urologic clinicians will utilize a troubleshooting checklist and an algorithm when difficult urinary catheter or traumatic catheters are encountered in order to promote improved patient care. Our goal in this strategy would be to provide better nursing education through urology lead seminars on catheter placement and provide resources when troubleshooting difficult catheter insertions. We would ideally see improvement in healthcare costs by having less traumatic catheter insertions and the complications that result. Prospectively, traumatic or DUC consults will be tracked at our hospitals before initiating the protocol.

FOOTNOTES

Author contributions: Sarver J, Farley R, Daugherty S, Bilbrew J, and Palka J performed the research, contributed ideas, analyzed the date, and wrote the manuscript; Sarver J revised the manuscript. All authors have read and approve the final manuscript.

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Informed consent statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

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ORIGINAL ARTICLE

Retrospective Study

Epidemiological trends in diabetic renal complications in United States adults: A center for disease control and prevention wide-ranging online data for epidemiologic research analysis (1999-2020)

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Abstract

BACKGROUND

Renal complications of diabetes mellitus pose a significant public health challenge, contributing to substantial morbidity and mortality globally. Understanding temporal trends and regional disparities in mortality related to diabetic nephropathy is crucial for guiding targeted interventions and policy decisions.

AIM

To display the trends and disparities of diabetic nephropathy related mortality.

METHODS

A retrospective analysis was conducted using death certificate data from the center for disease control and prevention (CDC) wide-ranging online data for epidemiologic research analysis (WONDER) database, spanning from 1999 to 2020, to investigate mortality related to renal complications of diabetes in adults aged 35 or above. Age-adjusted mortality rate (AAMR) per 100000 persons and annual percent change (APC) were computed, with stratification by year, sex, race/ethnicity, and geographic region.

RESULTS

Between 1999 and 2020, a total of 525804 deaths occurred among adults aged 35 to 85+ years due to renal-related issues associated with diabetes. AAMR for renal-related deaths in adult diabetic patients showed a consistent increase from 1.6 in 1999 to 34.9 in 2020 (average APC [AAPC]: 17.23; 95% confidence interval [CI]: 13.35-28.79). Throughout the study period, men consistently had higher AAMR (overall AAMR for men: 17.8; 95%CI: 17.7-17.9). In 1999, the AAMR for men was 1.8, increasing to 44.2 by 2020 (AAPC: 17.54; 95%CI: 13.09-29.53), while for women, it was 1.6 in 1999 and rose to 27.6 by 2020 (AAPC: 15.55; 95%CI: 13.35-21.10). American Indian/Alaska Native adults exhibited the highest overall AAMR (36.1; 95%CI: 35.2-36.9), followed by Black/African American (25.5; 95%CI: 25.3-25.7). The highest mortality was observed in the Western (AAMR: 16.6; 95%CI: 16.5-16.7), followed by the Midwestern region (AAMR: 14.4; 95%CI: 14.314.4). Significant variations in AAMR were observed among different states, with Oklahoma recording the highest (21.2) and Connecticut the lowest (7). The CDC WONDER database could potentially have omissions or inaccuracies. It does not provide data outside of the available variables. Furthermore, dataset after 2020 was not included in this study.

CONCLUSION

Our findings highlight an alarming rise in mortality related to renal complications of diabetes among United States adults over the past two decades, with concerning disparities across demographic and geographic factors. These results underscore the urgent need for targeted interventions, policies, and protocols to address the growing burden of diabetic nephropathy and substantially reduce mortality rates in the United States. This will help improve the overall health outcome in the United States by identifying communities at risk and implementing tailored assistance to them.

Key Words: Kidney diseases; Mortality; Chronic disease; Comorbidity; Diabetes mellitus

Core Tip: This study focused on investigating renal complications of diabetes mellitus through implementing a large United States database. Our analysis aimed to display mortality rates resulting from renal complications of diabetes on a large scale. The results showed gender, racial, and geographic disparities with higher mortality risk in male patients, native Indian/Alaskan, western states, and nonmetropolitan areas. These disparities emphasized on the importance of involving and encouraging healthcare stakeholders to take further action to improve healthcare specially for vulnerable populations.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder associated with elevated blood sugar levels and subsequent insulin dysfunction. DM can damage both macro- and microvasculature, causing complications that impact various body organs, including the kidneys[1]. Diabetic kidney disease (DKD) is a highly prevalent complication of DM, often resulting in chronic kidney disease and end-stage renal disease[2]. The progression of DKD is influenced by factors such as obesity, hypertension, poor glycemic control, and the complex interplay of genetic, environmental, and lifestyle factors[3,4]. In the United States, diabetic nephropathy is the leading cause of renal disease, contributing significantly to morbidity and mortality in the affected individuals, with a prevalence between 20% and 40% among diabetic patients[5].

Approximately 7% of the United States population have DM[6], and renal failure is listed as the cause of death in 6%-12% of adults with DM. The incidence of renal diseases has increased significantly in the diabetic population as compared to the nondiabetic population[7]. The prevalence of diabetic nephropathy remains a strong predictor of morbidity and mortality in diabetic patients[8]; hence, there is an urgent need to understand the trends associated with DKD related mortality in hopes to drastically reduce the mortality rate in the United States population. The existing knowledge gap will be covered by understanding these patterns as we will gain insight into the various aspects that contribute to the increased morbidity and mortality associated with diabetic nephropathy. We will be able to identify high risk regions and direct focused assistance towards these communities to help alleviate the burden of DKD. The present study aimed to examine the United States mortality trends from 1999 to 2020, using advanced statistical methods to assess the link between DM-related renal complications and mortality, while considering the influence of other factors. The results of our study will provide crucial insights for public health interventions and policy-making, guiding targeted interventions to reduce diabetic nephropathy-related mortality among the adult population in the United States.

MATERIALS AND METHODS

Data source

The center for disease control and prevention (CDC) wide-ranging online data for epidemiologic research analysis (WONDER) database was used to collect data from death certificates[9]. The study analyzed death incidents of adults secondary to diabetes-related renal complications between 1999 and 2020 utilizing the International Classification of Diseases and Related Health Problems 10th version (ICD-10) codes E10.2, E11.2, E12.2, E13.2, and E14.2[10]. The study looked at death records from the Multiple Cause-of-Death Public Use registry to find the incidence of diabetes-related renal complications. Renal complications of diabetes were listed as a contributing factor or as the primary cause of death in these cases. The research did not require permission from a regional institutional review board since it relied on deidentified public use data provided by the government. The STROBE standards for reporting observational research were followed in this study[11].

Data abstraction

The population number, year, place of death, demographic features, geographical breakdown, state-specific statistics, and distinction between urban and rural areas are all included in the dataset. The location of death consists of various places, including hospitals, houses, hospices, nursing homes, and long-term care institutions. The term "demographics" refers to information on gender, age, race, and ethnicity. The following are the categories for race and ethnicity: White, Black/African American, Latino, American Indians/Alaska Natives, and Asian/Pacific Islanders.

According to the National Centre for Health Statics Urban-Rural Classification Scheme, the population was divided into urban areas (which included large metropolitan areas with a population of 1 million or more, as well as medium/small metropolitan areas with a population ranging from 50000 to 999999), rural areas (with a population of less than 50000), and other counties in the 2013 United States Census[12]. Additionally, the Northeast, Midwest, South, and West regions are categorized into four distinct geographical groups according to standards set by the United States Census Bureau[13].

Statistical analysis

We analyzed the mortality rate per 100000 individuals for both unadjusted and age-adjusted data across the period from 1999 to 2020 to investigate regional trends in mortality related to acute renal failure. These rates were divided into categories based on year, gender, race/ethnicity, state, and urban/rural status. The crude mortality rates were determined by dividing the total number of acute renal failure deaths by the corresponding United States population each year [14]. Age-adjusted mortality rates (AAMR) were calculated by standardizing diabetes-related renal complications death in the United States in 2000[15]. The annual percent change (APC) and its associated 95% confidence interval (CI) in AAMR were calculated using the Join-Point Regression Program (Version 5.0.2, National Cancer Institute)[16]. This study was carried out to analyze annual changes in diabetes-related renal complications mortality at the national level[17]. This approach utilizes log-linear regression models to detect meaningful alterations in AAMR. The APCs were classified as increasing or decreasing if the slope reflecting changes in mortality differed substantially from zero, as assessed by two-tailed *t*-testing[18]. A significance level of $P < 0.05$ was used to establish statistical significance. Additionally, a sensitivity analysis was conducted for fatalities of diabetes-related renal complications ("E10.2, E11.2, E12.2, E13.2, E14.2"), which were identified as the primary cause of death.

RESULTS

Diabetes-related renal complications in adult patients caused a total of 525804 deaths in the United States between 1999 and 2020 (Supplementary Table 1). Of these, 39.78% occurred within medical facilities, 30.42% at home, 20.55% in nursing homes/long-term care facilities, 5.72% in hospices, and 3.42% at other places (Supplementary Table 2).

AAMR exhibited a consistent upward trend from 1999 until the study's conclusion in 2020; 1.6 to 34.9, respectively (average APC [AAPC]: 17.23; 95%CI: 13.35-28.79). AAMR slightly increased from 1999 to 2010 (APC: 16.69; 95%CI: -33.79-165.4) followed by a marked increase from 2010 to 2013 (APC: 55.08; 95%CI: 4.27-72.62) and slow increase from 2013 to 2018 (APC: 1.56; 95%CI: -4.03-53.29), and then it again increased dramatically from 2018 to 2020 (APC: 13.71; 95%CI: 3.95-20.90) (Figure 1, Supplementary Tables 3 and 4).

Adult men had consistently higher AAMR than adult women throughout the study period (overall AAMR for men: 17.8, 95%CI: 17.7-17.9; women: 11.2, 95%CI: 11.1-11.2). In 1999, the AAMR for adult men was 1.8, which steadily increased to 9.2 in 2010 (APC: 17.77; 95%CI: -36.74-99.34), followed by a dramatic increase to 30.8 in 2013 (APC: 48.95; 95%CI: -1.52-65.02), and by 2020, it increased to 44.2 (APC: 5.89; 95%CI: 1.02-16.18). For adult women, the AAMR in 1999 was 1.6, which steadily increased to 6 in 2010 (APC: 15.62; 95%CI: -25.63-27.41), followed by a dramatic increase to 20.5 in 2013 (APC: 52.10; 95%CI: 31.49-68.29), and by 2020 it increased to 27.6 (APC: 2.60; 95%CI: 0.27-4.69). The AAMR for adult men and women in 1999 was 1.8 and 1.6, respectively, which increased to 44.2 and 27.6 in 2020 (men: AAPC: 17.54, 95%CI: 13.09-29.53; women: AAPC: 15.55, 95%CI: 13.35-21.10) (Figure 1, Supplementary Tables 3 and 4).

When stratified by race/ethnicity, AAMR was highest among American Indian/Alaska Native, followed by Black/African American, Hispanic, Asian/Pacific Islander, and White populations (overall AAMR for American Indian/Alaska Native: 36.1, 95% CI: 35.2-36.9; Black/African American: 25.5, 95%CI: 25.3-25.7; Hispanic: 22.5, 95%CI: 22.4-22.7; Asian/Pacific Islander: 15.4, 95%CI: 15.2-15.6; White: 11.4, 95% CI: 11.4-11.5).

The AAMR of American Indian/Alaska Natives slightly decreased from 1999 to 2005 (APC: -2.79; 95%CI: -30.45-12.84), followed by a significant increase from 2005 to 2013 (APC: 35.91; 95%CI: 29.51-55.89), and then steadily increased from 2013 to 2020 (APC: 4.73; 95%CI: 1.78-7.60).

The AAMR trend of Black/African American, Asian/Pacific Islander, and White followed the same pattern, progressively increasing from 1999 to 2010 (Black/African American: APC: 17.48; 95%CI: -16.02-26.89; Asian/Pacific Islander: APC: 16.85; 95%CI: -22.56-28.84; White: APC: 16.74; 95%CI: -40.94-35.73), followed by a dramatic increase from 2010 to 2013 (Black/African American: APC: 47.73; 95%CI: 25.1-63.27; Asian/Pacific Islander: APC: 45.58; 95%CI: 2.88-60.93; White: APC: 51.76; 95%CI: 6.27-70.78), and then increased till 2020 (Black/African American: APC: 3.91; 95%CI: 0.26-7; Asian/Pacific Islander: APC: 4.57; 95%CI: 0.79-9.22; White: APC: 4.42; 95%CI: 2.08-7.06).

The AAMR of Hispanics/Latinos steadily increased from 1999 to 2009 (APC: 11.18; 95%CI: -1.32-9.22), followed by a massive increase from 2009 to 2013 (APC: 50.33; 95%CI: 28.09-70.14), then gradually decreased from 2013 to 2018 (APC: -0.47; 95%CI: 7.71-11.91), and finally increased from 2018 to 2020 (APC: 17.16; 95%CI: 5.35-26.04) (Figure 2A, Supplementary Tables 3 and 5).

A significant difference in AAMR was observed in different states, with the AAMR ranging from 21.2 (95%CI: 20.8-21.7) in Oklahoma to 7 (95%CI: 6.8-7.3) in Connecticut. States falling into the top 90th percentile were Kentucky, Minnesota, Mississippi, Nebraska, Oklahoma, Oregon, South Dakota, Washington, and West Virginia, which had approximately two times the AAMR compared to states that fell into the lower 10th percentile, namely, Connecticut, Florida, Illinois, Massachusetts, Nevada, New Jersey and New York (Figure 2B, Supplementary Table 6).

On average, throughout the study period, the highest mortality was observed in the Western (AAMR: 16.6; 95%CI: 16.5-16.7), followed by the Midwestern region (AAMR: 14.4; 95%CI: 14.314.4), Southern (AAMR: 14.1; 95%CI: 14-14.2), and Northeastern regions (AAMR: 9.9; 95%CI: 9.8-10) (Figure 2C, Supplementary Table 7).

Nonmetropolitan areas had consistently higher AAMR than metropolitan areas throughout the study period, with an overall AAMR of 16 (95%CI: 15.9-16.1) and 13.5 (95%CI: 13.4-13.5), respectively. AAMR of nonmetropolitan steadily ascended from 1999 to 2009 (APC: 14.80, 95%CI: -5.31-22.87), followed by a dramatic increase from 2009 to 2013 (APC: 47.93, 95%CI: 34.62-67.98), and then slightly increased till 2020 (APC: 5.41, 95%CI: 2.46-8.19). Similarly, the AAMR of metropolitan areas steadily ascended from 1999 to 2010 (APC: 16.23, 95%CI: -34.35-192.1), followed by a dramatic increase from 2010 to 2013 (APC: 54.49, 95%CI: 1.78-72.14), followed by a slight increase from 2013 to 2018(APC: 1.40, 95%CI: -4.32-55.78), and then again significantly increased from 2018 to 2020 (APC: 13.48, 95%CI: 3.47-20.85) (Figure 2D, Supplementary Tables 3 and 8). Figure 3 is a central illustration of the trends in Demographics and Disparities in Renal Complications in our study population (Figure 3).

DISCUSSION

The results of our study offer valuable insights into the evolving trends of mortality associated with renal complications among diabetic patients in the United States through the past two decades, from 1999 to 2020. Previous research examining mortality trends linked to diabetic nephropathy has similarly pointed towards an increase in mortality rates [19]. We analyzed national mortality data to explain patterns, disparities, and potential contributing factors to guide preventive strategies and improve clinical management for this vulnerable population.

Our analysis showed that men consistently exhibited higher AAMR compared to women throughout the study period. AAMR varied across racial/ethnic groups, with the highest rate among the American Indian/Alaska Native population. Geographically, significant differences in AAMR were evident among states and regions, with Western states and nonmetropolitan areas consistently showing higher AAMR throughout the study period.

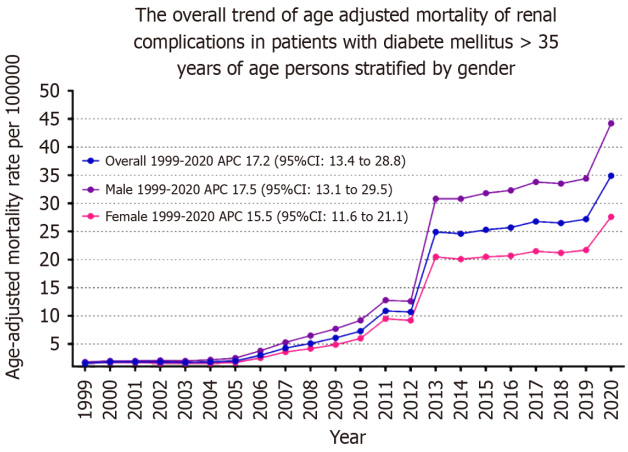

Figure 1 Overall and sex-stratified deaths due to renal complications in diabetic patients: Age-adjusted mortality rates per 100000 in adults in the United States, 1999–2020. APC: Annual percent change.

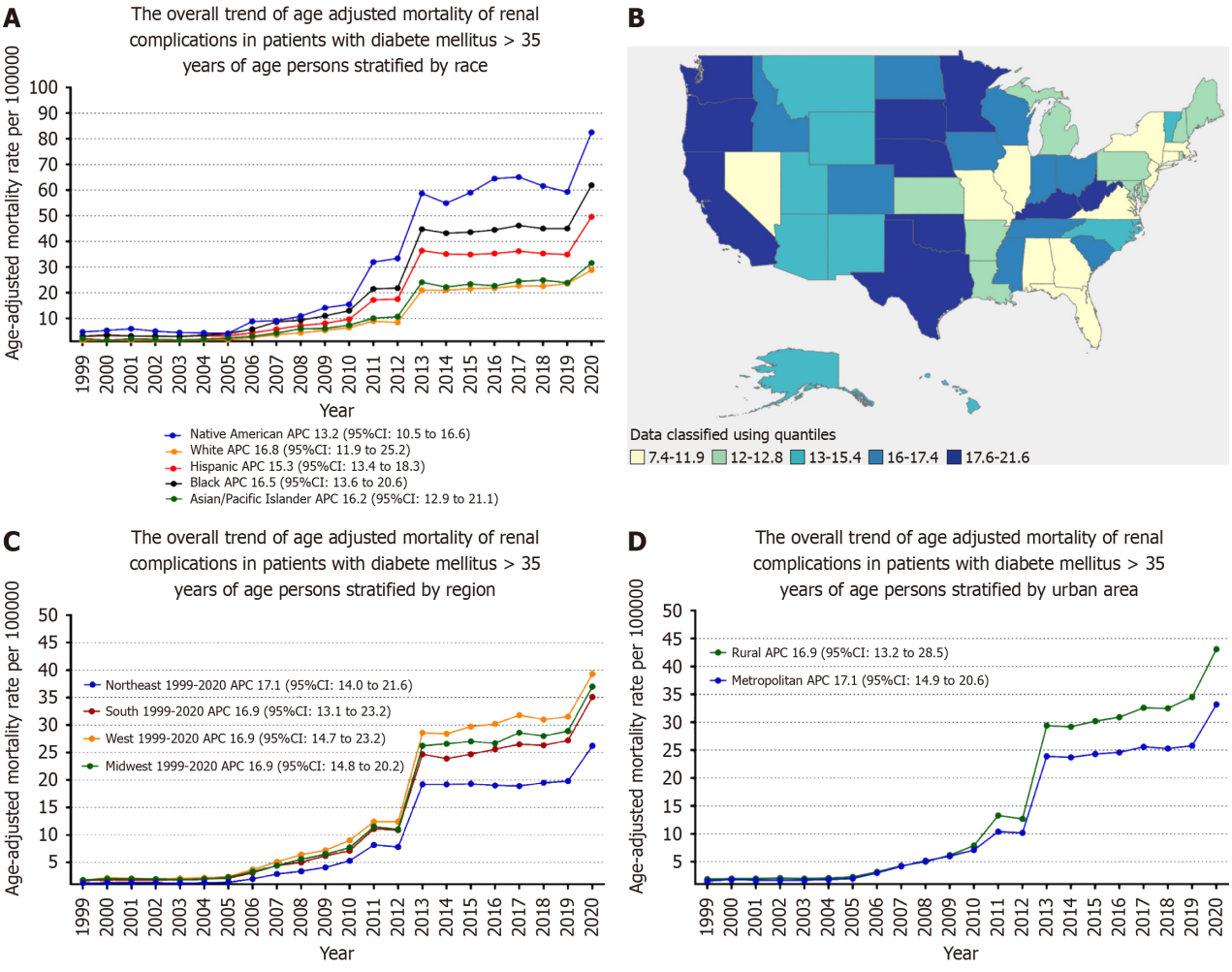

Figure 2 Age-adjusted mortality rates per 100000 related to renal complications in diabetic patients in the United States, 1999 to 2020. A: Stratified by race; B: Stratified by states; C: Stratified by census region; D: Stratified by urbanization. APC: Annual percent change.

The continuous upward trend in AAMR observed over the years likely stems from a complex interplay of factors, including the increasing disease prevalence, longer disease duration, suboptimal glycemic control, presence of comorbidities, healthcare access, and quality issues, as well as environmental and lifestyle factors[20].

The analysis revealed a consistent pattern of higher AAMR among males than females throughout the study period. This gender disparity in the findings may be due to inherent biological elements, behavioral factors, healthcare utilization, and occupational exposure. Additionally, men tend to engage in more hazardous behavior, such as unhealthy

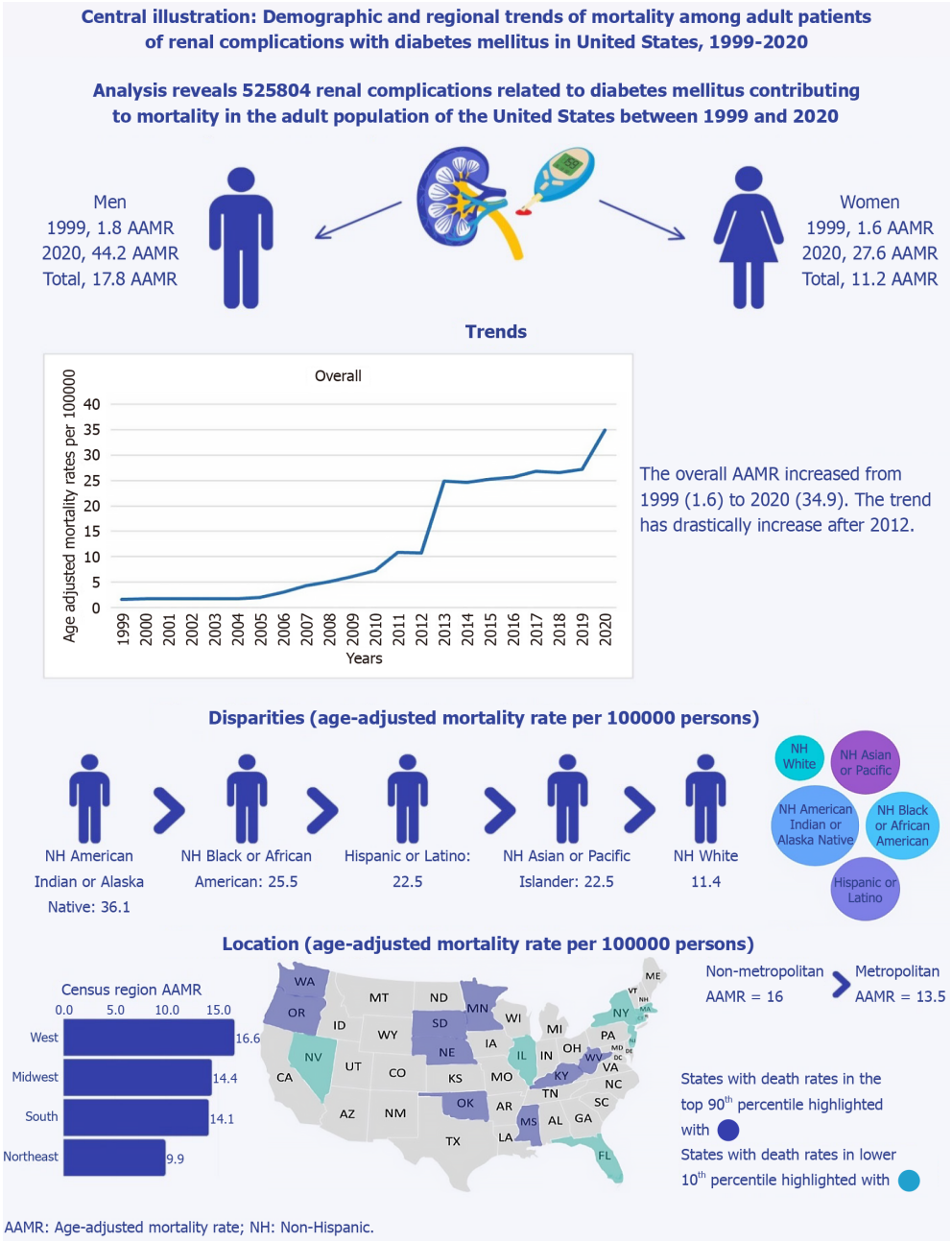

Figure 3 Central illustration: Trends in demographics and disparities in renal complications among adult diabetic patients in the United States: 1999 to 2020. AAMR: Age-adjusted mortality rate.

dietary habits and higher rates of smoking and alcohol consumption, which can exacerbate the progression of diabetes and its complications[21]. Furthermore, the gender disparity in the frequency of DKD in men and women could be attributed to hormonal differences. Studies have shown a reno-protective effect of estrogen and progesterone[22]. In diabetic nephropathy, depletion of the concentration of plasma estradiol is found with dysfunction of the signaling of the estrogen receptor[23]. Testosterone is associated with exacerbation of diabetic nephropathy[24].

Moreover, significant discrepancies in AAMR were observed across racial and ethnic groups, with American Indian/Alaska Native and white populations having the highest and lowest AAMR, respectively. The average life expectancy in the United States for American Indians is 72.8 years old, which is 6.9 years lower than that for white Americans[25]. These disparities may be influenced by genetic predispositions, cultural factors, and historical trauma, which may affect health behaviors and healthcare utilization, alongside socioeconomic disparities that encompass limited healthcare access and lower socioeconomic status. These factors are linked to a higher prevalence of health issues such as diabetes and a lower likelihood of rehabilitation success[26]. Studies have found that there is a sense of doubt and uncertainty amongst the elderly population of the American Indians particularly regarding the healthcare facilities and costs of healthcare services [27]. Low literacy levels, unemployment, and lack of adequate resources play a part in further promoting healthcare disparities in these populations[28]. Some additional key factors involved in the increased risk for diabetes and kidney disease in the American Indian population include poverty, over nutrition, poor health care, and high intake of sugar [29]. Moreover, higher rates of comorbidities within these communities, such as obesity and hypertension, contribute to

the increased burden of diabetic complications. Research consistently shows that American Indian children and adolescents have a higher prevalence of overweight and obesity compared to their white counterparts[30-32]. These high risk communities have an increased risk of metabolic syndrome as well. This, in turn, snowballs and leads to drastic complications associated with diabetes[33].

While exploring the genetic component of the increased mortality in this specific race, a genome wide association study was done in Pima Indians. A variant of 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase isoform 2 (PFKFB2), which is important in glucose metabolism, was identified. This variation appears to increase the risk of diabetic nephropathy [34]. Further aspects of gene expression in American Indians/Alaska Natives remain largely unexplored and efforts are consistently being made. The Traditional Food Project is an initiative to prevent diabetes in American Indian/Alaska Native communities. It recognizes that traditional foods and food sovereignty are important areas to address the public health issues of chronic disease[35].

In addition, we also observed significant geographical variations in AAMR, with the Western region having the highest-burden compared to other United States regions, and it may occur because of macro social determinants of health [36]. The western region of the United States, especially in rural areas, faces significant challenges in accessing quality healthcare[37,38]. These challenges are exacerbated by economic instability, leading to higher poverty rates and an aging population[36]. Factors such as distance to healthcare facilities and overall satisfaction with care can influence the preference for a particular healthcare source[39]. Studies show that older ethnic minorities in rural communities are at increased risk for diabetes complications[40]. Most of these people in western rural United States have low literacy rates, minimal household income, and an inherent inability to afford healthcare services that are not easily accessible to them. All of these factors contribute significantly to the elevated mortality consistent with our findings.

Nonmetropolitan areas consistently recorded higher AAMR than metropolitan areas over the study period. This trend can be attributed to several interrelated factors. First, nonmetropolitan regions often face limited access to healthcare resources, including fewer hospitals, specialists, and medical services[41]. Consequently, residents may experience delays in receiving essential medical treatment, leading to adverse health outcomes and, ultimately, higher mortality rates. Second, nonmetropolitan areas frequently grapple with health disparities stemming from socioeconomic factors such as poverty, lower education levels, and a higher prevalence of unhealthy behaviors like smoking and poor diet choices[42]. These disparities contribute to a higher burden of chronic diseases and overall worse health outcomes in these areas. Additionally, nonmetropolitan populations tend to be older, as younger individuals often migrate to urban centers in search of opportunities[43]. The aging population is with increased risk of age-related health issues, contributing to increased mortality rates. Environmental factors, such as exposure to pollution from agricultural activities or limited access to clean water sources, can also exacerbate health challenges in nonmetropolitan areas[44,45].

Furthermore, the shortage of healthcare providers and lack of infrastructure contribute to inadequate healthcare delivery and management of health conditions. Lastly, unhealthy lifestyle choices such as substance abuse and a sedentary lifestyle are more prevalent in nonmetropolitan regions, further compounding the health risks faced by residents[46,47]. Addressing these complex challenges requires comprehensive strategies that encompass improving healthcare access, socioeconomic conditions, public health interventions, and infrastructure development tailored to the unique needs of the nonmetropolitan communities.

Our study showed significant disparities in AAMR due to renal complications of diabetes across different states, ranging from 7 in Connecticut to 21.2 in Oklahoma. Several factors contribute to these disparities. Access to healthcare stands out as a critical determinant, with states offering better access to specialized clinics and timely screenings likely experiencing lower mortality rates[48]. Socioeconomic factors such as income, education, and insurance coverage further exacerbate these differences, as individuals with higher socioeconomic status often have better access to resources and healthcare services. Cultural values, dietary habits, and lifestyle choices also influence outcomes, with states embracing healthier habits potentially experiencing lower mortality rates[49].

Comorbidities such as obesity have been extensively researched and the results consistently prove that the prevalence of type 2 diabetes and its complications increases exponentially in the presence of these additive factors. This also includes hypertension as diabetes-related kidney disease is significantly higher in hypertensive population[50]. Additionally, diabetic nephropathy is associated with an increased risk of cardiovascular disease[51]. These multiple chronic conditions together contribute to the high rates of morbidity and mortality with DKD.

Our study further cemented the statement that DKD is a significant cause of morbidity and mortality. According to a previous study using population based National Health and Nutrition Examination Survey (NHANES), the ratio of prevalence of DKD adjusted for age, sex, race/ethnicity in 2005-2008 was 1.34 (1.11-1.61) and 0.98 (0.87-1.10) among the United States general population and persons with diabetes, respectively. The trend established for DKD in the general United States population was statistically significant (P = 0.003), but for the diabetic population, it was not statistically significant (P = 0.77)[52]. Hence, it is imperative to establish a trend that is evidence based. Our study validated the previous literature stating that diabetic nephropathy is one of the critical consequences in diabetic population. It further categorizes it and provides vital insight into the patterns and identifies high risk communities.

Addressing these multifaceted elements is imminent when defining guidelines for combatting the increasing prevalence of diabetes-related kidney disease. This can only be achieved through targeted interventions. Focusing on better healthcare access and monitoring the high risk population at regular intervals with a predetermined protocol is crucial. Early screening will play a pivotal role in decreasing the disease burden associated with DKD[33]. These policies are absolutely critical to narrowing the gap in AAMR due to diabetes-related renal complications across regions and improving outcomes among individuals with diabetes nationwide.

The study faced several limitations that merit attention. First, it relied primarily on the CDC WONDER database which records death certificates but may have inaccuracies or omissions. The stratification of years in the database is such that we used 1999-2020 for our study to include two decades worth of data to establish a trend with the most available

evidence; hence, any data after 2020 was not included. Additionally, AAMR was calculated using the 2000 United States population as the standard population, and no other standard populations were used. Moreover, the study exclusively focused on individuals aged 35 and above, potentially overlooking variations in younger age groups. Interpretation of trends may have been influenced by unaccounted factors, introducing biases in the conclusions. Furthermore, the lack of clinical data, such as specific biomarkers and clinical parameters, treatment methods, lab results, or therapeutic approaches, made it challenging to comprehend the increase in fatalities. The lack of detailed subgroup analyses for different occurrences of diabetes-related renal complications resulted in a knowledge gap, hindering the identification of underlying causes for rising death rates. Data on the socioeconomic status, including income level and insurance coverage, was not available in the database, which impedes the clear recognition of disparities in healthcare access. The potential confounders including differences in healthcare access, medication adherence, and lifestyle factors may have influenced the trends. Lastly, any changes in the use of ICD-10 coding practices over time could have impacted the mortality trends.

CONCLUSION

This analysis of renal complications of diabetes-related mortality data spanning 1999 to 2020 reveals an increasing trend in AAMR at an alarming rate, emphasizing the burden on public health. These findings highlight the significant disparities that exist across racial and ethnic groups and gender. The highest AAMR was observed in American Indian/Alaska Natives and men, respectively. Additionally, geographic differences play an impact, as seen with the consistently higher AAMR observed in nonmetropolitan regions and Western states. The disproportionate impact on these groups demands immediate attention. To combat this escalating threat to public health, it is imperative to implement focused interventions and enhance healthcare accessibility especially in the high risks communities to alleviate the deepening burden of renal complications associated with diabetes. These policies will enhance overall health outcomes nationwide.

FOOTNOTES

Author contributions: Muhammad AN and Eltawansy S contributed to methodology; Ali A contributed to software; Azeem B and Kashan M contributed to validation; Afzaal Z and Ahmed M contributed to formal analysis; Aman K and Amanullah A contributed to investigation; Naveed Uz Zafar M contributed to data curation; Lajczak P and Obi O contributed to the writing of the original draft.

Institutional review board statement: Researchers are not required to obtain explicit consent from participants as a national database was used with deidentified patient information.

Informed consent statement: Informed consent was waived due to using a national database.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest related to this work.

Data sharing statement: Data available within the article or its Supplementary materials. The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary materials.

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ORIGINAL ARTICLE

Clinical Trials Study

Sucroferric oxyhydroxide monotherapy for hyperphosphatemia in Indian chronic kidney disease patients undergoing hemodialysis: A phase IV, single-arm, open-label study

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Abstract

BACKGROUND

Hyperphosphatemia (HP) is a common complication in an advanced stage of chronic kidney disease (CKD) and is associated with cardiovascular issues, metabolic bone abnormalities and worsening of secondary hyperparathyroidism. Most patients on dialysis require phosphate binders to control HP. Sucroferric oxyhydroxide (SO) (Dynulta™) is a calcium-free, polynuclear iron (III) based oral phosphate binder, for the treatment of HP. In this phase IV, open-label, single-arm, multi-center, 12-week, SOLO CKD study evaluated efficacy and safety of Dynulta™ in Indian CKD patients undergoing hemodialysis.

AIM

To investigate the efficacy, safety and tolerability of SO Chewable Tablet

(Dynulta™) in patients with CKD on hemodialysis.

METHODS

Hyperphosphatemic patients on hemodialysis and fulfilling eligibility criteria were included in the study for at least 12 weeks and received SO 1500 mg chewable tablet per day. The key endpoint was change in mean serum phosphorus levels after 12 weeks. Data were analysed using analysis of variance, Paired test, Wilcoxon test, and post-hoc comparisons, with $P < 0.05$ considered statistically significant, using Graph Pad software.

RESULTS

A total of 114 patients were enrolled and 94 patients completed the study. The mean ± SD serum phosphorous level was reduced from 7.62 mg/dL ± 2.02 mg/dL at baseline to 5.13 mg/dL ± 1.88 mg/dL after 12 weeks of treatment. At each follow-up visit, the reduction in mean serum phosphorous levels was statistically significant (P value < 0.05) compared to baseline, confirming the efficacy of SO. A total of 33.33% of patients experienced adverse events (AEs). The most frequently reported AEs were pyrexia, nasopharyngitis and headache, which were considered unlikely to be related to the study drug treatment. No serious AEs was reported during the study period and no patients discontinued treatment due to AEs.

CONCLUSION

This first real-world study in Indian CKD patients on hemodialysis shows SO as a safe, and effective monotherapy for HP, though its small sample size limits generalizability.

Key Words: Chronic kidney disease; Dynulta™; Hemodialysis; Hyperphosphatemia; Iron-based phosphate binder; Sucroferric oxyhydroxide

Core Tip: This is the first research study on the use of Sucroferric oxyhydroxide (SO) in Indian patients and also marks the first such study from the Southeast Asia region. The study was a single-arm study, registered with the Clinical Trials Registry India. The positive results from this study will add to the growing body of evidence, primarily generated in the United States and European Union, supporting the efficacy of SO in the Asian population.

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INTRODUCTION

Hyperphosphatemia (HP) is a frequent consequence of end stage renal disease (ESRD) caused by the inability of the kidney to excrete excess phosphate[1]. Regulation of phosphorus excretion by the kidney is the key mechanism of maintaining body's phosphate balance[2].

Nearly 90% of hemodialysis patients need to take oral phosphate binders, and 40%–50% of them still have increased phosphate levels after treatment[3]. Available oral phosphate binders are associated with a range of limitations and side effects. Although effective, aluminium-based binders are no longer extensively utilized due to the slow accumulation of absorbed aluminium in tissues. Although affordable and efficient, calcium-based salts may contribute to the progression of vascular calcification. Sevelamer carbonate, a calcium free phosphate binder, is widely used to reduce serum phosphate levels in patients with advanced chronic kidney disease (CKD)[4]. Sucroferric oxyhydroxide (SO) had a numerically lower mean daily pill burden and better treatment adherence than sevelamer carbonate[5]. Pill burden is a particularly important consideration, because patients receiving dialysis are often required to take a large number of concomitant tablets each day. Indeed, lower pill burden is associated with increased adherence to phosphate binders, and high level of medication adherence is associated with increased control of serum phosphorus[6].

SO is an oral, iron-based, non-calcium phosphate binder, formulated as a chewable tablet (500 mg iron equivalent to 2500 mg SO). It is composed of sucrose, starches and the active moiety, polynuclear iron (III)-oxyhydroxide (pn-FeOOH). SO displays effective phosphate binding across a wide pH range in the gastrointestinal (GI) tract, with minimal systemic absorption and no evidence of iron accumulation even after long term use[6,7]. Phosphate binding occurs through ligand exchange between hydroxyl groups and/or water molecules and phosphate ions, maintaining efficacy throughout the physiological pH range of the GI tract[8]. In phase I clinical studies, SO was well tolerated and associated with minimal GI iron absorption[9,10]. A phase II study demonstrated that doses of 1.0−2.5 g/day (based on iron content) substantially reduced serum phosphorus concentrations and reaffirmed its tolerability profile[11]. In a phase III study conducted in

multiple sites across Europe, the United States, Russia, Ukraine, and South Africa, the phosphorus-lowering effect of SO was shown by demonstrating its non-inferiority to sevelamer carbonate and superiority to an ineffective control[12]. An extension of the phase III study confirmed the long-term efficacy of SO which was maintained over 1 year[13]. SO is available as a treatment option for patients in United States, Europe, Japan, Australia and Canada. In India it was approved in 2020[7].

Studies from various parts of India provide some background, even though the precise prevalence of CKD and dialysis patients in particular regions is unknown. For example, a study conducted in Delhi found that the prevalence of CKD was 7852 per million people (pmp), but studies conducted in Chennai and Bhopal found that the prevalence at the community level was 8600 pmp, and the incidence of ESRD was 151 pmp. In India, there are about 700 dialysis facilities and 4000 dialysis machines, most of which are in the private sector and mostly found in cities. Currently, there are an estimated 20000 dialysis patients nationwide. These facts aid in placing the study's sampling in context by showing how CKD patients and dialysis recipients are distributed throughout India[14].

In the present study we aimed to evaluate the efficacy, safety and tolerability of SO chewable tablet in controlling serum phosphorus concentration after 12 weeks of treatment in patients with CKD on hemodialysis.

MATERIALS AND METHODS

Study design

This was a phase IV, prospective, multi-center, single arm, open label study in CKD patients with HP who were on maintenance hemodialysis. The study was conducted at four clinical sites located in Bangalore, Mysore, Delhi and Agra, providing a diverse representation of urban and rural populations across India in accordance with regulatory and ethical guidelines (Declaration of Helsinki, ICH GCP, and New Drug and Clinical Trial Rule 2019). The study protocol and protocol related documents were approved by the institutional ethics committee before initiating the trial related activity and written informed consent was obtained from all individual participants included in the study. The study was registered with Clinical Trials Registry of India (Clinical Trials Registry India//2021/07/034812). Study flow chart is presented in Figure 1.

Study patients

The potential participants were screened and the eligibility of the patients were determined on the basis of inclusion and exclusion criteria. A total of 114 adult patients of either sex with CKD aged > 18 years, providing informed consent, receiving maintenance hemodialysis for at least 12 weeks prior to screening, have a history of HP and serum phosphorus levels > 5.5 mg/dL (> 1.78 mmol/L) at screening constituted the study population. Enrolled patients were on a diet standardized by dietician throughout the study. All patients were dialyzed on high flux dialyzer and remained on same dialyzer throughout the entire study duration.

Patients were excluded who were taking any interfering medications like oral calcium supplements, any drugs/agents having a phosphate binding action that contain aluminium, magnesium or calcium (apart from antihyperkalaemic drugs), phosphate binders, sevelamer carbonate, nicotinamide, oral iron products, oral vitamins containing iron and other oral iron containing supplement or they stopped medication and screened after 1 week of washout. Dietary compliance was assessed at every visit post enrolment. Patients were excluded who had intact parathyroid hormone (iPTH) levels > 800 ng/L (> 800 pg/mL or 88 pmol/L) at screening, planned or expected parathyroidectomy within the next 6 months, serum total calcium > 10.5 mg/dL (> 2.6 mmol/L) or < 7.6 mg/Dl (< 1.9 mmol/L) at screening, any history of major GI surgery, clinically significant active GI disorders, swallowing difficulties/dysphagia, estimated life expectancy of less than 12 months, anticipated renal transplantation during study participation, history of haemochromatosis or other iron accumulation disorders that might lead to iron overload and raised alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of the normal range at screening.

Treatment

In cases where the patient was already taking medications for HP, those medications were stopped at least 1 week before the administration of study drug. After the start of this study, patients were instructed to administer chewable SO tablets 500 mg of Emcure Pharmaceuticals Limited, India orally three times a day before meals. Dose increase or decrease of 500 mg/day (1 tablet/day) was permitted, provided a patient had received that dose for a minimum of 2-4 weeks until an acceptable serum phosphorus level reached, with regular monitoring for efficacy, safety or tolerability reasons at any time. Treatment compliance was assessed *via* daily diary recordings as well as tablet counts.

Study visits

Total study duration for each enrolled patient was maximum 93 days (7 days for screening and 84 days ± 2 days of treatment). Patients reported to the study center four times for evaluation of study parameters: (1) During the screening (valid up to 7 days prior to day of enrolment); (2) Enrolment visit 1 (Day 1); (3) Visit 2 follow-up visit (week 4, Day 28 ± 2); (4) Visit 3 follow-up visit (week 8, Day 56 ± 2); and (5) The end-of-study (EOS) visit 4 (week 12, Day 84 ± 2).

Blood sampling was conducted four times to measure serum phosphorus levels. Other laboratory parameters were measured at the screening visit and at the EOS visit, including complete blood count (CBC), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), glucose, serum calcium, and iPTH.

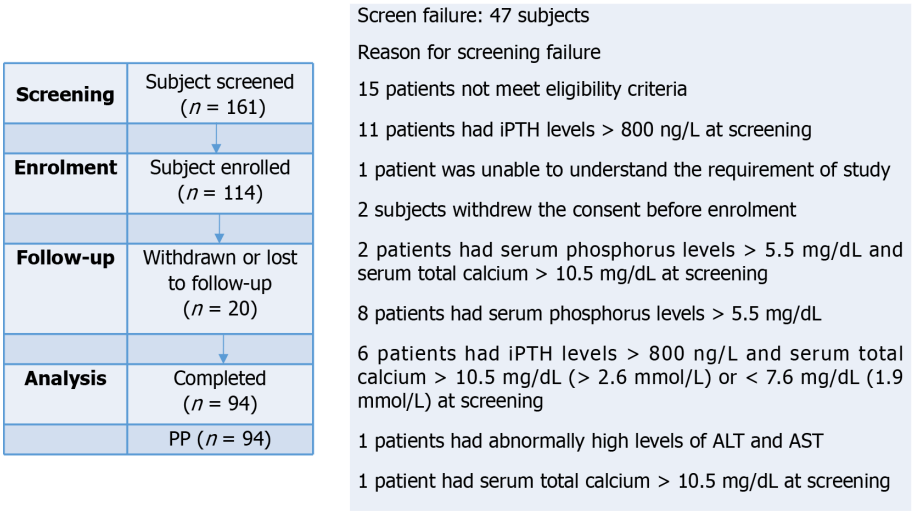

Figure 1 Study flow chart. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IPTH: Intact parathyroid hormone; PP: Per protocol.

Sample size

Based on a power of 90% and a type I error rate of alpha = 0.05 (2-tailed), a sample size of at least 93 patients was required to detect a clinically acceptable difference of 0.3 mmol/L in mean change in serum phosphorus level from baseline after treatment with a SD of 0.63 mmol/L based on previously published study[15]. Considering dropout rate of 20%, adjusted sample size was 117 patients required to draw conclusion of study. Thus, total sample size including dropout rate was 117 patients.

Statistical analysis

The primary efficacy variable was change in mean serum phosphorus level from baseline to each visit. Using per protocol (PP) population principle, patients were analysed. The PP-population was defined as all patients who were enrolled as per entry criteria and completed the study in compliance with the protocol. Safety was evaluated on the basis of the number of adverse events (AEs), as well as their seriousness, severity, and causality. Additionally, at week 12, changes from baseline of other laboratory parameters (CBC, SGOT, SGPT, glucose, serum calcium, serum iPTH) and vital signs and physical findings were recorded. All data were expressed as the mean ± SD. Statistical analyses were performed with analysis of variance (ANOVA)/Paired test/Wilcoxon test based on the normality of data followed by post-hoc individual comparisons (for repeat measures ANOVA) *vs* baseline. $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using Graph Pad (version 9.4.1) software.

RESULTS

All 114 enrolled patients received SO, of whom 94 patients completed 12 weeks' treatment (Figure 1). Age of patients who were enrolled in this study was found to be in a range of 23 years to 72 years with a mean age of 49.67 years ± 11.63 years, mean height and weight of patients were 162.91 ± 7.79 centimeters and 60.95 kg ± 10.08 kg respectively. The most common etiologies of CKD observed were hypertension (82.46%) and diabetes mellitus (31.57%) among the study patients presented in Table 1.

Efficacy analysis

The decrease in mean serum phosphorus at each follow-up visit was statistically significant ($P < 0.05$) compared to baseline, reducing from 7.62 mg/dL at baseline to 5.13 mg/dL at the end of the study confirming, the efficacy of the SO treatment (Table 2). Serum phosphorous levels were significantly declined by day 28, with continued reductions observed at day 56 and day 84 (Figure 2). By the end of study treatment, a substantial proportion of patients achieved the target serum phosphorus level of < 5.5 mg/dL and a noteworthy percentage achieved levels < 4.5 mg/dL at week 12 (Table 3).

Safety analysis

A total of 83 adverse reactions occurred in 38 of 114 patients (33.33%), with the most frequent being pyrexia (23.68%), nasopharyngitis (14.91%) and headache (12.28%). AEs were classified as mild (40.61%) to moderate (59.32%) in severity with no events showing a definite causal relationship with SO. Only five AEs were considered possible/probably related to the study drug, including vomiting ($n = 1$) and diarrhea ($n = 4$), as shown in Table 4. No serious adverse event was found during the study and no patients discontinued the study due to a treatment emergent adverse event.

Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) remained within clinically acceptable limits by the end of study period.

Table 1 Demographics and clinical characteristics of the patients at baseline (*n* = 114), *n* (%)

Characteristics	
Gender	
Male	62 (54.39)
Female	52 (45.61)
Age (years)	
≥ 65	9 (7.89)
≤ 65	105 (92.11)
Body mass index (kg/m^2) (mean ± SD)	22.96 ± 3.37
Asian race	114 (100)
Dialysis history	
< 1 year	38 (33.33)
≥ 1 year and < 3 years	39 (34.21)
≥ 3 years	37 (32.46)
Presence of complication	
Hypertension	94 (82.46)
Diabetes mellitus	36 (31.57)
Anemia	1 (0.88)
Coronary artery disease	3 (2.63)
Hyperthyroidism	1 (0.88)
Thyroid	1 (0.88)

Table 2 Comparison of serum phosphorus response to baseline phosphorus at each visit (*n* = 94)

Visit	mean ± SD	*P* value (compared to baseline)
Serum phosphorus (mg/dL)		
Per protocol population (*n* = 94)		
Screening visit: Day 7 to Day 1	7.62 ± 2.02	-
Follow-up visit: Day 28	6.37 ± 2.33	$P < 0.05$
Follow-up visit: Day 56	5.49 ± 2.19	$P < 0.05$
End of study visit: Day 84	5.13 ± 1.88	$P < 0.05$
Change from baseline at Day 28	1.25 ± 1.55	$P < 0.05$
Change from baseline at Day 56	2.19 ± 2.07	$P < 0.05$
Change from baseline at Day 84	2.49 ± 2.13	$P < 0.05$

P value was analysed using Wilcoxon test.

Regarding laboratory parameters, a minor and statistically non-significant change in serum calcium levels was observed after 12 weeks of treatment ($P > 0.05$), as summarized in Table 5. A similar trend was seen for serum iPTH levels, which decreased slightly from baseline, but this change was also not statistically significant ($P > 0.05$). Moreover, no statistically significant changes were observed in CBC and the biochemical parameter from baseline to end of the study visit suggesting that SO did not have any negative effect on patients' general health condition.

DISCUSSION

In this study, the use of SO as a monotherapy effectively reduced serum phosphorus levels in patients with CKD

Table 3 Percentage of patients have < 5.5 mg/dL serum phosphorus (*n* = 94), *n* (%)

Visit	Percentage
Follow-up visit: Day 28	37 (39.36)
Follow-up visit: Day 56	50 (53.19)
End of study visit: Day 84	62 (65.96)

Table 4 Adverse events possibly or probably related to treatment (*n* = 114)

Preferred term	Frequency (%)
Diarrhea	3.51
Vomiting	0.88
Total	4.39

Table 5 Laboratory parameters at baseline and end of study (Day 84) (*n* = 94), *n* (%)

Parameter	Baseline (mean ± SD)	Day 84 (mean ± SD)	Change from baseline (mean ± SD)	*P* value (*vs* baseline)
Serum calcium (mg/dL)	8.87 ± 0.67	8.75 ± 0.90	0.12 ± 0.92	$P > 0.05$
Serum intact parathyroid hormone (pg/mL)	264.06 ± 196.70	236.89 ± 217.63	27.17 ± 150.89	$P > 0.05$
Hemoglobin (g/dL)	11.16 ± 2.11	11.36 ± 2.15	-0.21 ± 2.01	$P > 0.05$
Total red blood cell (million/cu.mm)	3.91 ± 0.92	4.19 ± 0.95	-0.28 ± 0.72	$P > 0.05$
Total white blood cell (cells/cu.mm)	7057.34 ± 2027.30	7341.11 ± 2010.73	-283.77 ± 2329.78	$P > 0.05$
Neutrophils	60.03 (10.42)	59.54 (11.38)	0.49 (12.69)	$P > 0.05$
Lymphocytes	29.35 (10.37)	29.57 (11.31)	-0.21 (10.81)	$P > 0.05$
Eosinophils	4.92 (3.75)	5.02 (4.14)	-0.10 (5.24)	$P > 0.05$
Monocytes	4.93 (2.40)	4.77 (3.06)	0.16 (2.92)	$P > 0.05$
Basophils	0.77 (0.35)	0.79 (0.43)	-0.01 (0.48)	$P > 0.05$
Platelet (thou/mm^3)	2.38 ± 0.77	2.41 ± 0.84	-0.03 ± 0.81	$P > 0.05$
Hematocrit	34.44 (9.18)	37.58 (22.40)	3.14 (23.27)	$P > 0.05$
Serum glutamic-oxaloacetic transaminase (U/L)	23.97 ± 15.52	28.29 ± 18.32	-3.85 ± 20.79	$P > 0.05$
Serum glutamic pyruvic transaminase (U/L)	21.22 ± 14.84	28.21 ± 24.59	-6.98 ± 25.58	$P < 0.05$
Glucose (mg/dL)	138.38 ± 72.24	124.70 ± 53.52	13.68 ± 63.44	$P > 0.05$

undergoing hemodialysis. A significant reduction ($P < 0.05$) in mean serum phosphorus levels was observed from baseline to end of the study and 65.96% of patients, achieved the target serum phosphorus level of < 5.5 mg/dL.

These results are consistent with those of Ramos *et al*[1] where a significant reduction in serum phosphate was observed during treatment with SO, with the proportion of patients achieving phosphate levels ≤ 5.5 mg/dL increasing from 41.3% to 56.2%–62.7% over 12 months. Similarly, in a United States database study involving 530 hemodialysis patients, the proportion of patients achieving target phosphate levels increased significantly from 17.7% at baseline to 36% after 1 year[1]. The same study also reported a 50% reduction in phosphate binder pill burden, from 8.5 pills per day to 4.0–4.3 pills per day.

Another 12 weeks' phase-III study supported these findings, showing that patients switching from sevelamer hydrochloride to SO at a lower dose (814 mg/day) experienced effective phosphate control with reduced pill burden[16].

The present study assessed serum iPTH levels, which remained stable throughout the treatment period. This finding is consistent with other studies where no significant difference in plasma PTH levels was reported following SO treatment [1].

We did not observe any statistically significant changes in serum calcium levels at the end of the study treatment period, which is in contrast to Ramos *et al*[1] who observed a statistically significant decrease in serum calcium at the first quarter (Q1) of treatment. However, calcium levels remained stable in later treatment periods (Q2, Q3, Q4).

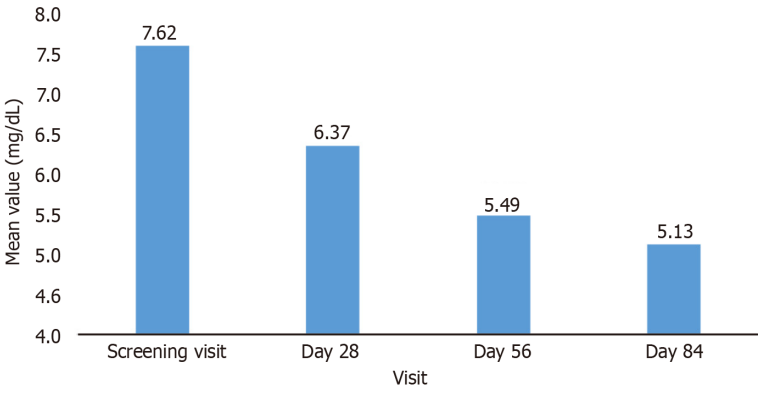

Figure 2 Level of serum phosphorus during each visit.

The safety profile of SO was favorable, with only 4.3% of AEs considered possible/probable related to the drug. The most common AE was diarrhoea, which aligns with previous studies that also identified diarrhea as the most frequently reported AE[16,17]. Importantly, no serious AEs occurred during the study.

Strengths of this study includes its prospective multi-center design, providing real-world evidence from an Indian population. The study was conducted over 84 days (approx 3 months) during which period, the dietary compliance and treatment adherence were closely monitored. Use of patient diary ensured treatment compliance as well recording AEs. Additionally, the study evaluated the impact of SO on various biochemical parameters, adding valuable data to the current literature.

However, there are several limitations to the study. The non-comparative single arm study design limits the ability to directly compare SO with other Phosphate binders/placebo. Furthermore, the relatively small sample size and regional focus may affect the generalizability of the findings, as dietary habits and population characteristics vary across different regions of India. Future research with larger sample sizes, longer follow-up, and comparisons to other phosphate binders is needed to confirm these findings and explore long-term outcomes.

CONCLUSION

In conclusion, this study establishes the efficacy of SO in reducing serum phosphorus levels in patients with CKD on hemodialysis while also establishing its safety and tolerability in Indian patients. These findings suggest that SO, as a monotherapy, can be an effective treatment option for managing HP in this patient population, with the added benefit of reduced pill burden.

While the results are promising more extensive research in different parts of India with larger sample sizes and comparator arms are required to generate more robust data and therefore a treatment's wider applicability in the Indian population. SO is positioned as a safe and effective monotherapy treatment option for CKD-associated HP due to its favorable safety profile and lower pill burden.

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FOOTNOTES

Author contributions: Niranjan MR, Gupta V, Srinivasa S and Bhalla AK contributed to the execution of the research, data analysis, statistical analysis, manuscript preparation and manuscript editing and review; Gaikwad A was involved in the conceptualization and study design, manuscript preparation, and manuscript editing and review; Wangikar P, Suryawanshi S and Gajbe P contributed to manuscript preparation, and manuscript editing and review; all of the authors read and approved the final version of the manuscript to be published.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee, Institutional Ethics Committee, ECR/1512/Inst/KA/2021; Institutional Ethics Committee, Mysore Medical College and Research Institute and Associate Hospital, ECR/134/Inst/KA/2013/RR-19; Pushpanjali Hospital Ethics ECR/1235/Lnst/UP/2019; and Ethics Committee Sir Ganga Ram Hospital, ECR/20/Inst/DL/2013/RR-19.

Clinical trial registration statement: The study was registered with Clinical Trials Registry of India, https://ctri.nic.in/Clinicaltrials/Login.php (Clinical Trials Registry India//2021/07/034812).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Gaikwad A, Wangikar P, Suryawanshi S and Gajbe P are employees of Emcure Pharmaceuticals, India.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: We did not use CONSORT (for reporting a randomised trial).

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ORIGINAL ARTICLE

Observational Study

Assessment of chronic kidney disease and associated factors at Wolkite University Specialized Hospital: A cross-sectional study

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Abstract

BACKGROUND

Kidney is the vital organ that plays a great role in maintaining an optimal internal environment. The normal kidney function can be altered by physical injury or disease. Currently, chronic kidney disease (CKD) is an increasing major health problem worldwide. In 2017, it was ranked as the 12th leading cause of death and is expected to rise to the 5th ranked cause of death by 2040. Therefore, early detection, increasing patients' awareness and treatment of CKD are required to hold the problem. However, despite its higher prevalence of hospitalized morbidity and mortality, little is known about the magnitude and associated factor of CKD in the Ethiopian context. Hence this study aimed to determine the magnitude of CKD and associated factors at Wolkite University Specialized Hospital (WKUSTH), South West Ethiopia.

AIM

To determine the magnitude, and associated factors of CKD in WKUSTH, Ethiopia.

METHODS
Institutional based cross-sectional study with secondary data was conducted from November 15, 2021 to February 28, 2022 at WKUSTH. Three hundred forty five (345) participants were selected by a convenient sampling technique. Creatinine and urea were measured using cobas311 fully automated chemistry analyzer and estimated glomerular filtration rate (eGFR) was calculated using CKD epidemiology collaboration formula. Socio-demographic and clinical data were collected by using a pretested questionnaire. Data were coded and entered into EpiData 3.1 version and exported to STATA version 14 for analysis. Bivariate analysis was used to screen candidate variables for multivariate analysis. In the multivariate analysis a P value < 0.05 were considered statistically significant.

RESULTS
The magnitude of CKD by impaired eGFR were 54 (15.7%) (95%CI: 0.116-0.194). In multivariable analysis, older age [adjusted odds ratio (AOR) = 5.91, 95%CI: 2.41-14.47)], hypertension (AOR =10.41, 95%CI: 4.55-23.81), diabetes mellitus (AOR = 5.90, 95%CI: 2.14-16.23), high body mass index (AOR = 3.0, 95%CI: 1.30-7.27), and anemia (AOR = 2.94, 95%CI: 1.26-6.88) were independently associated with CKD.

CONCLUSION
The magnitude of CKD among adult patients admitted to WKUSTH was high. Hence, researchers need to do a population-based study and longitudinal study on the magnitude of CKD, associated factors. Estimation of GFR for all hospitalized patients might help to early detection of CKD and prevent complications.

Key Words: Chronic kidney disease; Glomerular filtration rate; Magnitude; Associated factor; Kidney

Core Tip: The core tip of this manuscript is to assess chronic kidney disease (CKD) and associated factors at Wolkite University Specialized Hospital. Accordingly, during admission 54 (15.7%) medical ward admitted patients with 95%CI: 0.116-0.194) had CKD by impaired estimated glomerular filtration rate (eGFR). While during discharge 71 (20.58%) medical ward admitted patients with 95%CI: 0.165-0.249) of the patients had CKD by impaired eGFR. This implies about 4.95% of the admitted patients develop kidney disease in hospital during their stay. Therefore, especially, for this resource limited country, screening of kidney disease for admitted patients is essential.

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INTRODUCTION

The kidneys are highly active metabolic organs that are essential for preserving a stable internal environment. One of their primary functions is regulating the body's fluid and electrolyte balance through processes such as filtration, reabsorption, and the elimination of waste products[1]. The kidneys generate urine through glomerular filtration, followed by the tubular reabsorption of solutes and water. However, physical injury or disease can disrupt this normal function, potentially resulting in acute or chronic kidney disease (CKD)[2]. A slow decline of kidney function or persistent kidney dysfunction can lead to CKD[3].

CKD is a non-communicable disease characterized by kidney damage or a glomerular filtration rate (GFR) below 60 mL/minute/1.73 m² for a minimum of three months[4]. When the kidneys become damaged, they lose their ability to effectively filter blood and eliminate waste, resulting in the buildup of toxic substances and excess fluid in the body[5]. A GFR of less than 60 mL/minute/1.73 m² serves as the primary biomarker for impaired kidney function, while a urine albumin-to-creatinine ratio greater than 30 mg/g is the key indicator of kidney damage[6].

A GFR below 60 mL/minute/1.73 m² indicates a loss of at least half of kidney function and is linked to a higher risk of systemic complications[7,8]. Therefore, assessing GFR is valuable for the early detection of renal impairment, monitoring kidney function, and determining appropriate drug dosages[9]. Creatinine clearance is the typical method for determining GFR, which is calculated from serum creatinine concentration, a 24-hour collected urine creatinine concentration, and a 24-hour measured urine volume. However, the feasibility of precise urine collection is a major limitation of creatinine clearance as a measure of GFR; hence, GFR is mathematically estimated. For this study, CKD epidemiology collaboration (CKD-EPI) equation is used to estimate GFR[9].

Globally, the burden of CKD is on the rise, leading to increased hospitalization, morbidity, and mortality[10]. In 2017, 1.2 million people were died from CKD with estimated increment of this number up to 4.0 million in a worst-case scenario by 2040 and it was ranked as the 12th leading cause of death in 2017 and is anticipated to become the 5th leading

cause by 2040[11]. CVD, hypertension, anemia, malnutrition, and mineral and bone disorders are some of the complications of CKD[12].

CKD is a significant public health issue and poses a substantial economic burden. It leads to higher hospitalization rates, increased morbidity, premature mortality, and reduced productivity for both patients and their caregivers[13,14]. Patients with CKD also have a high risk of progression to end-stage renal disease (ESRD). The management of ESRD is extremely costly, as it necessitates either dialysis or a kidney transplant[6]. Undergoing dialysis imposes a significant burden, both in terms of reduced quality of life and financial costs[15]. In developed nations, the treatment of ESRD accounts for over 2%-3% of their yearly healthcare budget[16]. Their annual medical expenses for managing ESRD range from $20110 to $100593 per patient[13].

Even though both the incidence and prevalence of CKD appear to be increasing globally, the rate of increase is much higher in African countries; this is probably a result of poverty, a high incidence of non-communicable and communicable diseases, hazardous work, poor education, and inaccessible or unaffordable treatment[16,17]. Approximately 12%-23% of adults in sub-Saharan Africa (SSA) have CKD. However, due to its asymptomatic nature, early diagnosis at a treatable stage is often missed, increasing the risk of progression to ESRD. Once ESRD develops, survival depends on either dialysis or transplantation. However, due to limited access and the high costs of these treatments, only 1.5% of SSA patients in need of renal replacement therapy receive it[18].

Thus, early detection of CKD is crucial, especially in this resource-limited country, where access to renal replacement therapy is severely restricted, to help prevent or slow its progression to ESRD. However, despite its high prevalence and its subsequent increased hospitalized morbidity and mortality, there is a scarcity of data in Ethiopia especially in study area hospitalized patients. Hence, the finding of this research will serve as a foundational step for future research, such as longitudinal or community-based studies.

MATERIALS AND METHODS

Study design, setting and population

A facility based cross-sectional study with secondary data was conducted from November 15, 2021, to February 28, 2022, in Wolkite University Specialized Hospital (WKUSTH). WKUSTH is located in the Central Ethiopia, Gurage Zone, Wolkite located 158 km South West of the capital city of Ethiopia, Addis Ababa, on the way to Jimma. The hospital is situated in Gubreye sub-city, 14 km east of Wolkite town. Currently, WKUSTH is offering outpatient, inpatient, surgical, gynecological, and pediatric services.

Aged 18 years or older patients admitted to the medical wards of WKUSTH during the study period and signed on the consent sheet were included. However, patients on the intensive care unit who were unconscious, younger than 18 years old, amputated patient, pregnant women, admitted due to malnutrition, or morbidly obese patient were excluded. The sample size was determined by using a single population proportion formula [$N = (Z\alpha/2)^2 \times P \times (1\text{-}P)/d^2$] with an assumption of a 95% confidence level, a 5% margin of error (d), (P = 33.9%) prevalence CKD at Desse referral hospital, Ethiopia[19], (N) = $(1.96)^2 \times 0.339 \times (0.661)/(0.05)^2$, ($N$) = 345. During the study period, 997 patients were admitted to the adult medical ward. From these admitted patients, a total of 345 patients were selected using consecutive sampling technique.

Data collection procedure and technique

Experienced nurses and laboratory professionals were trained on the study protocol and data collection format. After detailed information about the study was given, written consent was obtained from all subjects who were included in the study. Data were collected from patients and their medical charts using a pretested, semi-structured face-to-face interview questionnaire that was developed from the World Health Organisation STEPS surveillance manual[20]. The data collection tool contains socio-demographic information, clinical information, lifestyle behaviors, anthropometric measurements, blood pressure measurements, and laboratory findings. Patients were interviewed to collect data on socio-demographic characteristics, clinical information, and lifestyle behaviors by a trained nurse. The clinical information of the patient or comorbidities, like hypertension, diabetes mellitus (DM), cardiovascular disease, and human immunodeficiency virus/acquired immunodeficiency syndrome information, was confirmed by reviewing their medical chart.

Trained clinical nurses took blood pressure and performed anthropometric measurements. After measuring each subject's height and weight, the body mass index (BMI) for each was determined by dividing the weight in kg by the height in m^2 and categorized as normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥ 30 kg/m^2). Following at least ten minutes of rest, the patient's blood pressure was measured, and hypertension was defined as being on antihypertensive medication (history of hypertension) or having a systolic and/or diastolic blood pressure ≥ 140/90 mm/Hg. All comorbidities were defined as present if they were documented in the medical records.

Seven mL of venous blood was collected during admission and discharge by trained laboratory professional following standard operation procedure. Five mL of the blood was collected in each study participant during admission and discharge in sterile serum-separating tubes. The collected sample was left to form a clot at room temperature for 30 minutes, and then centrifuged. Biochemical tests such as creatinine and urea levels were analyzed by using cobas c 311 analyzer (cobas-roche Company, Germany) automated clinical chemistry analyzer according to the manufacturer's instructions and procedures in the laboratory. CKD-EPI Creatinine Equation (2021) was used to calculate GFR. Those having estimated GFR (eGFR) < 60 ml/min/1.73 m^2 both during admission and during discharge are considered as having CKD. Two ml of the blood was collected by EDTA tube for hemoglobin determination and determined using CELL DYNE 1800 hematology analyzer and Anemia is defined as hemoglobin < 13 g/dL in men and < 12 g/dL in

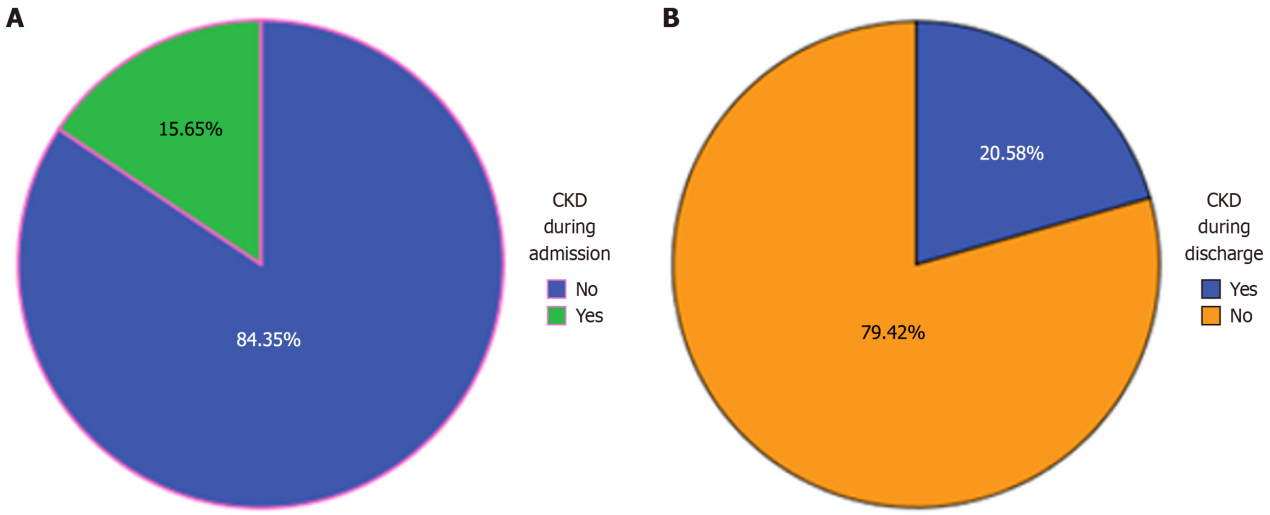

Figure 1 Magnitude of chronic kidney disease by impaired estimated glomerular filtration rate. A: Magnitude of chronic kidney disease (CKD) by impaired estimated glomerular filtration rate (eGFR) during admission among medical ward admitted patients at Wolkite University Specialized Hospital (WKUSTH), South West Ethiopia, 2022; B: Magnitude of CKD by impaired eGFR during discharge among medical ward admitted patients at WKUSTH, South West Ethiopia, 2022. CKD: Chronic kidney disease.

women. All laboratory measurements were done following the standard procedures recommended by the manufacturer.

Statistical analysis

Data were coded and entered into EpiData version 3.1 for further data cleaning and to allow consistency and eliminate discrepancies. Then after, it was exported to STATA version 14 software for analysis. Both bivariate and multivariate logistic regression was done. All Variables with a *P* value of less than 0.25 in the bivariate analysis were included in multivariate logistic regression. A *P* value < 0.05 was considered statistically significant. Finally, the result was presented using figures, charts, and table.

Data quality control

Questionnaire data quality control was assured by reviewing and checking for errors, completeness, accuracy, and consistency during data collection and before entry into EpiData, and corrective measures were taken. A pretest was done on 5% of the sample size in Butajira hospital. The expiration date of the reagents and lipemic and hemolysis of every sample were checked. Both normal and pathological control was done every day before sample analysis.

RESULTS

Socio-demographic characteristics

A total of 345 individuals participated with 100% response rate. Of the participants, 176 (51.0%) were male, 154 (44.64%), were in the age group above 59 years. The age (mean + SD) of the study participant was 51.64 years ± 17.73 years. Two-third of the participants 216 (62.6%) live in the rural area. About 249 (72.2%) of the study participants were married. Regarding educational status, 160 (46.4%) of the study participants had no formal education. Gender illustrates CKD higher in the male participants 29 (53.7%) than female 25 (46.3%). CKD was also more common on aged admitted patients compared to the counterparts [42 (77.8%) *vs* 12 (22.2%)] (Table 1).

Clinical and behavioral characteristics

In this study, the primary clinical diagnosis for admission was hypertension, accounting for 86 cases (24.97%), followed by anemia with 82 cases (23.8%), diabetes with 53 cases (15.4%), and cardiac issues with 38 cases (11.0%). CKD was more prevalent among participants with hypertension (39 cases, 72.2%), DM (21 cases, 38.9%), and those who were overweight (28 cases, 51.9%) (Table 2).

Magnitude of CKD

Creatinine levels were measured upon both admission and discharge. At admission, 54 out of the total participants (15.7%) (95%CI: 0.116-0.194) were diagnosed with CKD based on impaired eGFR (Figure 1A). However, by discharge, the number of CKD patients identified by impaired eGFR increased to 71 (20.58%) (95%CI: 0.165-0.249) (Figure 1B). This suggests that approximately 4.9% of admitted patients may have developed acute kidney injury (AKI) during hospitalization. Thus, the prevalence of CKD in this study is 15.7% (95%CI: 0.116-0.194). When categorized by disease stage, the distribution of CKD cases was as follows: (1) Stage 3a: 11 (20.37%); (2) Stage 3b: 22 (40.74%); (3) Stage 4: 20 (37.04%); and

Table 1 Socio-demographic characteristics of the study participant (*n* = 345), at Wolkite University Specialized Hospital, South West Ethiopia, 2022, *n* (%)

Variable	Category	Chronic kidney disease			*P* value
		Yes (*n* = 54)	No (*n* = 291)	Total	
Age	18-59	12 (22.2)	179 (61.5)	191 (55.4)	0.000
	≥ 60	42 (77.8)	112 (38.5)	154 (44.6)	
Sex	Male	29 (53.7)	147 (50.5)	176 (51.0)	0.389
	Female	25 (46.3)	144 (49.5)	169 (49.0)	
Place of residence	Urban	18 (33.3)	111 (38.1)	129 (37.4)	0.305
	Rural	36 (66.7)	180 (61.9)	216 (62.6)	
Marital status	Married	38 (70.4)	211 (72.5)	249 (72.2)	0.431
	Single	16 (29.6)	80 (27.5)	96 (27.8)	
Place of residence	Urban	52 (39.4)	31 (36.9)	83 (38.4)	
	Rural	80 (60.6)	53 (63.1)	133 (61.6)	
Educational status	Illiterate	33 (61.1)	127 (43.6)	160 (46.4)	0.093
	Primary	8 (14.8)	76 (26.1)	84 (24.3)	
	Secondary	10 (18.5)	59 (20.3)	69 (20)	
	Diploma and above	3 (5.6)	29 (10)	32 (9.3)	
Religion	Christian	29 (53.7)	105 (36.1)	134 (38.8)	0.012
	Muslim	25 (46.3)	186 (63.9)	211 (61.2)	
Occupation	Unemployed	6 (11.1)	31 (10.7)	37 (10.7)	0.539
	Government	5 (9.3)	29 (10)	34 (9.9)	
	Private	11 (20.4)	81 (27.8)	92 (26.7)	
	Farmer	29 (53.7)	120 (41.2)	149 (43.2)	
	Daily labor	2 (3.7)	13 (4.5)	15 (4.3)	
	House wife	1 (1.9)	17 (5.8)	18 (5.2)	

(4) Stage 5: 1 (1.85%) (Figure 2).

Factors associated with CKD

Before performing logstic regration, the assumptions of the model were verified. The first assumption is that the dependent variable must be categorical. Another assumption is absence of multicollinearity which refers to the relationship among the independent variables. In order to check the existence of multicollinearity, variance inflation factor (VIF) and tolerance (TOL), are calculated and presented in Table 3 below. To confirm the absence of multicollinearity, the value of VIF and TOL should be less than ten and one respectively. As it is shown in the Table 3 below, the value of VIF and TOL are less than ten and one respectively, which implies multicollonearity is not a problem and all the independent variables can be inserted in to the regression model together.

The Omnibus Tests of Model and Hosmer and Lemeshow test are the reliable indication of model fitness in logistic regression. They are interpreted differently. In order to be the model is fit, Omnibus Tests of Model should be significant while Hosmer and Lemeshow test should be insignificant. Accordingly as shown in Tables 4 and 5 below, the value for Omnibus Tests of Model is 0.000 and the Hosmer-Lemeshow Test is 0.542 respectively. So we can conclude that the model is fit.

After testing the assumptions, bivariate and multivariate logistic regression analyses were conducted to assess the relationship between dependent and independent variables. In the bivariate analysis, several factors showed a significant association with CKD at P <0.25 and were included in the multivariable analysis. These factors included age ≥ 60 years [crude odds ratio (COR) = 5.59, 95%CI: 2.82-11.08], a family history of CKD (COR = 7.32, 95%CI: 1.89-28.22), history of hypertension (COR = 13.49, 95%CI: 6.89-26.44), DM (COR = 5.15, 95%CI: 2.66-9.95), cardiac problems (COR = 3.37, 95%CI: 1.59-7.11), alcohol consumption (COR = 2.92, 95%CI: 1.28-6.61), cigarette smoking (COR = 3.46, 95%CI: 1.29-9.24), BMI ≥ 25 (COR = 3.78, 95%CI: 2.05-6.97), and anemia (COR = 4.29, 95%CI: 2.33-7.89). In the multivariable analysis, older age (adjusted odds ratio (AOR) = 5.91, 95%CI: 2.41-14.47), history of hypertension (AOR = 10.41, 95%CI: 4.55-23.81), DM (AOR = 5.90, 95%CI: 2.14-16.23), high BMI (AOR = 3.0, 95%CI: 1.30-7.27), and anemia (AOR = 2.94, 95%CI: 1.26-6.88) remained independently associated with CKD (Table 6).

Table 2 Clinical and behavioral characteristics of the study participant (*n* = 345) at Wolkite University Specialized Hospital, South West Ethiopia, 2022, *n* (%)

Variable	Category	CKD			*P* value
		Yes (*n* = 54)	No (*n* = 191)	Total	
Family history of CKD	Yes	7 (13.0)	2 (0.7)	9 (2.6)	0.000
	No	47 (87.0)	289 (99.3)	336 (97.4)	
Hypertension	Yes	39 (72.2)	47 (16.2)	86 (24.9)	0.000
	No	15 (27.8)	244 (83.8)	259 (75.1)	
diabetes mellitus	Yes	21 (38.9)	32 (11.0)	53 (15.4)	0.000
	No	33 (61.1)	259 (89.0)	292 (84.6)	
Cardiac problem	Yes	11 (20.4)	27 (9.3)	38 (11.0)	0.020
	No	43 (79.6)	264 (90.7)	307 (89.0)	
Human immunodeficiency virus status	Yes	1 (1.9)	9 (3.1)	10 (2.9)	0.518
	No	53 (98.1)	282 (96.9)	335 (97.1)	
Alcohol consumption	Yes	10 (18.5)	21 (7.2)	31 (9.0)	0.012
	No	44 (81.5)	270 (92.8)	314 (91.0)	
Cigarette smoking	Yes	7 (13.0)	12 (4.1)	19 (5.5)	0.017
	No	47 (87.0)	279 (95.9)	326 (94.5)	
Body mass index	Normal	19 (35.2)	231 (79.4)	250 (72.5)	0.000
	Overweight	28 (51.9)	51 (17.5)	79 (22.9)	
	Obese	7 (13.0)	9 (3.1)	16 (4.6)	
Anemia	Yes	27 (50.3)	55 (18.9)	82 (23.8)	0.000
	No	27 (50.3)	236 (81.1)	263 (76.2)	

CKD: Chronic kidney disease.

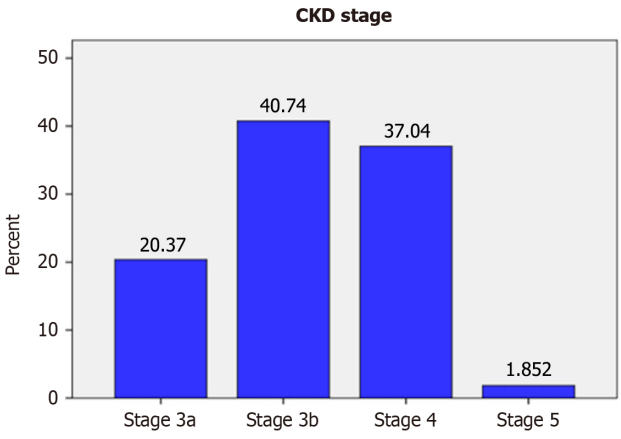

Figure 2 Stage of chronic kidney disease among medical ward admitted patients at Wolkite University Specialized Hospital, South West Ethiopia, 2022. CKD: Chronic kidney disease.

DISCUSSION

Currently, various factors such as lifestyle changes and the rising prevalence of non-communicable chronic diseases like hypertension and DM have contributed to CKD for becoming a significant global public health concern. Hospitalized patients, in particular, face a heightened risk of developing CKD due to various factors. In our study, the prevalence of CKD based on impaired eGFR was 15.65% at the time of admission, increasing to 20.58% at discharge. This indicates that approximately 4.9% of hospitalized patients develop kidney disease during their hospital stay. Therefore, screening for

Table 3 Multicollinearity test

Model		Collinearity statistics	
		Tolerance	Variance inflation factor
1	Sex	0.864	1.157
	Age	0.727	1.375
	Family member having chronic kidney disease	0.905	1.105
	History of known hypertension	0.864	1.157
	History of known diabetes mellitus	0.933	1.072
	History of heart problem	0.883	1.132
	Alcohol consumsion	0.858	1.165
	Cigarate smoking	0.910	1.099
	Anemia	0.915	1.093
	Occupation	0.612	1.635
	Education	0.570	1.755
	Body mass index	0.881	1.135
	Place of residence	0.561	1.782

Dependent variable: Chronic kidney disease.

Table 4 Omnibus tests of model coefficients

		χ^2	Df	*P* value
Step 1	Step	154.337	13	0.000
	Block	154.337	13	0.000
	Model	154.337	13	0.000

Table 5 Hosmer and Lemeshow test

Step	χ^2	Df	*P* value
1	6.952	8	0.542

kidney disease among admitted patients is crucial. Consequently, this study aimed to assess the prevalence and associated factors of CKD in adult patients admitted to the medical ward at WKUSTH.

Our study indicated that during admission, 54 (15.7%) of patients admitted to the medical ward had CKD based on impaired eGFR, with a 95%CI of 0.116-0.194. This finding was consistent with a study conducted in Botswana 16.3%[21], Uganda 15.3%[22], and London (17.7%)[23]. However, our results were higher than those reported in Canada 8.5%[24] and Brazil 12.7%[25]. This variation could be attributed to differences in population characteristics or a higher proportion of medically complex patients in our study. Conversely, studies from Spain (28.3%)[26], Germany (27.5%)[27], Kenya (38.6%)[28], Guinea (33%)[29], and Jimma University Medical Center (19.2%)[30] reported a higher prevalence of CKD compared to our findings. These discrepancies may be due to, studies conducted in Jimma University Medical Center, Kenya, Spain, and Guinea determined CKD using a single serum creatinine measurement, whereas our study utilized two serum creatinine measurements. This approach helped reduce the overestimation of CKD from 70 cases (20.19%) to 54 cases (15.7%).

In this study, factors associated to CKD included older age, a history of hypertension, DM, BMI, and anemia. Consequently, our findings indicate that hypertensive patients had an approximately tenfold higher risk of developing CKD compared to those without a history of hypertension. This result aligns with a study conducted in Uganda[22], Botswana[21], Kenya[28], Dessie[19], and Jimma[30]. This indicates that patients with previously known hypertensions have higher rates of renal complications.

Our study also identified DM (AOR = 5.90, 95%CI: 2.14-16.23) as a risk factor for CKD. Patients with diabetes had nearly six times the risk of developing CKD compared to those without diabetes. This finding was consistent with a study conducted in Brazil[25], Uganda[22], North-Central Nigeria[31], and Dessie referral hospital[19]. In this study, an age of

Table 6 Factors associated with chronic kidney disease using chronic kidney disease epidemiology collaboration equation among medical ward admitted patients using bivariate and multiple logistic regression in Wolkite University Specialized Hospital, South West Ethiopia, 2022

Variable	Category	CKD (*n*)		Crude OR (95%CI)	Adjusted OR (95%CI)	*P* value
		Yes	No			
Sex	Male	29	147	1.14 (0.63-2.03)		
	Female	25	144	1		
Age group	< 60	12	179	1	1	
	≥ 60	42	112	5.6 (2.82-11.08)	5.9 (2.41-14.5)	0.000
Residence	Urban	18	111	1		
	Rural	36	180	1.23 (0.66-2.27)		
Occupational status	Farmer	29	120	0.605 (0.34-1.08)		
	Other	25	171	1		
Educational status	Illiterate	33	127	0.943 (0.27-0.89)		
	Literate	21	164	1		
Family member having CKD	Yes	5	4	7.3 (1.89-28.22)	4.0 (0.70-23.19)	0.118
	No	49	287		1	
History of hypertension	Yes	39	47	13.5 (6.89-26.44)	10.4 (4.6-23.81)	0.000
	No	15	244		1	
History of diabetes mellitus	Yes	21	32	5.2 (2.66-9.95)	5.9 (2.14-16.23)	0.001
	No	33	259		1	
History of heart problem	Yes	13	25	3.4 (1.59-7.11)	1.7 (0.58-4.99)	0.33
	No	41	266		1	
Alcohol consumption	Yes	10	21	2.9 (1.28-6.61)	1.4 (0.46-4.31)	0.533
	No	44	270		1	
Cigarette smoking	Yes	7	12	3.5 (1.29-9.24)	1.9 (0.43-8.28)	0.399
	No	47	279		1	
Body mass index	< 25	19	231	1	1	
	≥ 25	35	60	3.8 (2.053-6.97)	3.1 (1.30-7.27)	0.010
Anemia	Yes	27	55	4.29 (2.33-7.88)	2.9 (1.26-6.88)	0.012
	No	27	236		1	

CKD: Chronic kidney disease; OR: Odds ratio.

over 60 years was independently linked to CKD. This finding aligns with previous studies conducted in Brazil[25], Kenya [28], Dessie referral hospital[19], northwest Ethiopia[32], and Jimma University Medical Center[30]. Age-related structural and functional changes in the kidneys or a higher prevalence of renal risk factors, like diabetes, hypertension, and heart disease attributed to the increment of CKD prevalence in aged patients.

Obesity was also identified as a risk factor for CKD, those patients having a BMI greater than 25 were being approximately three times more likely to develop the condition compared to those with a lower BMI. This finding was consistent with a study conducted in Cameroon [33], North-Central Nigeria[31], and Tigray teaching hospitals[34]. Anemia was also independently linked to CKD, aligning with findings from a study conducted in Kenya[28], other factors, such as a family history of kidney disease, a history of heart problems, alcohol consumption, and cigarette smoking, were significant only in the crude analysis.

Although this study has several strengths, it also has some limitations. Since it was conducted in a single hospital using a convenient sampling technique, the findings may not be fully generalizable to the entire population of admitted patients. Additionally, the cross-sectional study design limits our ability to establish a causal relationship between the assessed risk factors and CKD. Furthermore, potential confounding factors such as diet and medication use were not adequately controlled. There is also a possibility of misclassifying AKI as CKD. However, given that hospitalized patients are at a higher risk of developing CKD, our study attempted to diagnose the condition both at admission and discharge.

This approach may have helped reduce overestimation and misclassification of CKD.

CONCLUSION

This study found that the prevalence of CKD among adult patients admitted to the medical ward at WKUSTH was considerably high. Factors such as age over 60 years, high BMI, anemia, and comorbid conditions like hypertension and DM were significantly associated with CKD. Notably, all patients were unaware of their condition at the time of admission, suggesting a potentially high prevalence of kidney disease within the community. To gain a broader understanding, researchers should conduct community-based and longitudinal studies on outpatient populations, incorporating additional confounding variables such as diet and medication history. Estimating GFR for all hospitalized patients could facilitate early CKD detection and help prevent complications. Therefore, healthcare professionals and other stakeholders should provide health education on CKD risk factors, emphasize the benefits of early detection, and regularly monitor GFR in high-risk populations, including hypertensive, elderly, diabetic, anemic, and overweight or obese individuals.

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FOOTNOTES

Author contributions: Habtu BF conceived the study, prepared the proposal, analyzed the data, interpreted the findings, and wrote the manuscript; Habtu BF and Zuber H were participated in editing and revising subsequent drafts of the paper; Fanta O, Waqtola C, and Sintayehu A were involved in data analysis and reviewing of the manuscript; all authors reviewed the final version of the manuscript, and agree to be accountable for all aspects of the work.

Institutional review board statement: Ethical clearance was obtained from the ethical review board of Jimma University Institute of Health, No. IRHPGn/576/.

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ORIGINAL ARTICLE

Prospective Study

Modified National Early Warning Score 2, a reliable early warning system for predicting treatment outcomes in patients with emphysematous pyelonephritis

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Abstract

BACKGROUND

Emphysematous pyelonephritis (EPN) is a life-threatening necrotizing renal parenchyma infection characterized by gas formation due to severe bacterial infection, predominantly affecting diabetic and immunocompromised patients. It carries high morbidity and mortality, requiring early diagnosis and timely intervention. Various prognostic scoring systems help in triaging critically ill patients. The National Early Warning Score 2 (NEWS 2) scoring system is a widely used physiological assessment tool that evaluates clinical deterioration based on vital parameters, but its standard form lacks specificity for risk stratification in EPN, necessitating modifications to improve treatment decision-making and prognostic accuracy in this critical condition.

AIM

To highlight the need to modify the NEWS 2 score to enable more intense monitoring and better treatment outcomes.

METHODS

This prospective study was done on all EPN patients admitted to our hospital over the past 12 years. A weighted average risk-stratification index was calculated for each of the three groups, mortality risk was calculated for each of the NEWS 2

scores, and the need for intervention for each of the three groups was calculated. The NEWS 2 score was subsequently modified with 0-6, 7-14 and 15-20 scores included in groups 1, 2 and 3, respectively.

RESULTS

A total of 171 patients with EPN were included in the study, with a predominant association with diabetes (90.6%) and a female-to-male ratio of 1.5:1. The combined prognostic scoring of the three groups was 10.7, 13.0, and 21.9, respectively ($P < 0.01$). All patients managed conservatively belonged to group 1 ($P < 0.01$). Eight patients underwent early nephrectomy, with six from group 3 ($P < 0.01$). Overall mortality was 8 (4.7%), with seven from group 3 (87.5%). The cutoff NEWS 2 score for mortality was identified to be 15, with a sensitivity of 87.5%, specificity of 96.9%, and an overall accuracy rate of 96.5%. The area under the curve to predict mortality based on the NEWS 2 score was 0.98, with a confidence interval of (0.97, 1.0) and $P < 0.001$.

CONCLUSION

Modified NEWS 2 (mNEWS 2) score dramatically aids in the appropriate assessment of treatment-related outcomes. MNEWS 2 scores should become the practice standard to reduce the morbidity and mortality associated with this dreaded illness.

Key Words: Pyelonephritis; Emphysematous; Nephrectomy; National Early Warning Score 2; Mortality

Core Tip: We present the most extensive single-centre study on patients diagnosed with emphysematous pyelonephritis (EPN), comprehensively evaluating risk stratification, disease severity, and treatment outcomes. While the traditional National Early Warning Score 2 (NEWS 2) score is a well-established tool for triaging critically ill patients in emergency settings, its ability to predict long-term treatment outcomes in EPN remains limited. The modified NEWS 2 score proposed in this study enhances risk differentiation, allowing for more accurate prognostication and timely clinical decision-making. This refined scoring system enables optimized resource allocation, early intensive care unit admission, and tailored treatment approaches, ultimately improving patient survival and reducing morbidity in EPN.

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INTRODUCTION

Emphysematous pyelonephritis (EPN) is a commonly encountered urological emergency. The presence of gas in the renal parenchyma, collecting system, and peri/para nephric spaces causes a necrotizing infection that leads to severe sepsis-related complications. Historically, the mortality rate for EPN reached 78% in medically treated patients, with an overall mortality of 54%[1]. Recent studies, however, indicate a significant decline to approximately 20%–40%[2]. Standardized staging and prognostic scoring systems have facilitated early diagnosis, effective triage, and appropriate treatment, reducing morbidity and mortality[3-5].

With improved diagnostics and an ever-increasing awareness about this lethal disease, various authors looked at the next steps to improve the prognosis and further reduce the morbidity associated with EPN. Various inflammatory markers and scoring systems were looked into, and visible changes were observed in the management of EPN[6]. Focus has now shifted towards renal conservation therapy, with emphasis on early detection, internal (double J stenting) or external diversion [percutaneous nephrostomy (PCN) or drainage of peri-nephric collection][7-9].

Triaging such patients in the Emergency room is an essential pre-requisite. Emphasis should be placed on identifying those critically ill and those who need intensive care and early intervention. Urosepsis, gram-negative septicemia, Systemic inflammatory response syndrome (SIRS) and Multi-organ dysfunction syndrome are the dangerous sequelae of this dreaded condition. Once high-risk patients are identified, treating physicians must prioritize the treatment plans. Various scoring systems have helped identify and triage those high-risk individuals. Modified Early Warning score (MEWS), Pediatric Early Warning Score, National Early Warning Score (NEWS), and Sequential Organ Failure Assessment Score (SOFA) are to name a few[10-14]. National Early Warning Score 2 (NEWS 2) scoring is an improvised version of the NEWS score that advocates an objective system to standardize the evaluation and assessment of the clinical condition[15,16].

The Royal College of Surgeons of London introduced the original NEWS score in 2012[17,18]. The primary purpose was to detect and prioritize those who need acute emergency intensive care, as early detection, timely response and competent clinical responses are the three parameters that objectively define ultimate patient outcomes. The Royal

College redefined this scoring system in 2017 to enhance the precision of diagnosis and treatment. The NEWS 2 score is critical in identifying patients susceptible to clinical deterioration, prompting expedited care and medical/surgical intervention[19].

The NEWS 2 scoring system takes into consideration six physiological parameters. The readily available measures, ease of usability, lack of inter-observer variability, and higher degree of validity of the score have made it a popular triaging score in the emergency rooms of the United Kingdom and many other countries. Each has a score ranging from 0 to 3, with zero being the least severe and 3 being the most severe form. The NEWS 2 scoring system offers a tracking aid in assessing the patient's condition in an emergency setting and triaging geriatric patients in crowded emergency rooms[20-22].

The NEWS 2 score ranges from 0 to 20. A score of below 4 indicates a lower risk of clinical deterioration. Scores of 5 and 6 suggest a moderate risk of worsening, warranting an "urgent response threshold". The National Health Service of the United Kingdom, in association with The Royal College of Physicians, proposed a score of 7 as an "emergency response threshold" for triaging patients needing higher dependency unit or intensive care unit (ICU) monitoring[23]. While the NEWS 2 scoring system has been instrumental in the early detection of clinical deterioration and prioritizing emergency responses, its ability to predict treatment outcomes in severe infections like EPN remains suboptimal. A significant limitation lies in the broad risk stratification at higher scores—patients with a NEWS 2 score of 7 and those with a score of 20 are categorized similarly despite likely having vastly different prognoses and treatment responses. This lack of granularity in risk differentiation may lead to delayed or inappropriate allocation of critical care resources. Recognizing this limitation, we propose modifying the NEWS 2 system modified NEWS 2 (mNEWS 2) to enhance its predictive power by refining risk stratification, allowing for more precise triaging and early intervention. By tailoring the score to reflect clinical severity and response to treatment better, mNEWS 2 aims to bridge the gap between early warning and outcome prediction, ultimately improving decision-making and patient survival in EPN.

Though the NEWS 2 scoring system effectively detects clinical deterioration, its broad risk stratification at higher scores limits its ability to predict treatment outcomes in severe infections like EPN. Patients with scores of 7 and 20 are categorized similarly despite significant differences in clinical severity, which may lead to delayed or inappropriate critical care interventions. This study addresses this gap in knowledge by proposing a mNEWS 2 score that enhances risk differentiation, enables more precise triaging, prioritizes intensive monitoring and facilitates timely interventions in EPN cases.

MATERIALS AND METHODS

This study was conducted on all patients with EPNs admitted to our tertiary care referral teaching institution in South India between July 2012 and June 2024. Our study primarily evaluated clinical parameters and prognostic scoring in patients with EPN. Demographic attributes such as origin, ethnicity, and language were not specifically analyzed, as the objective was to assess risk stratification and treatment outcomes based on physiological and biochemical markers rather than population-based variations.

A list of all prognostic variables was tabulated from our institution's prospective database containing all those pre-defined prognostic variables. Prognostic scoring and risk stratification were done based on the author's previous published literature[4].

The prognostic scores were listed based on specific premeditated parameters. A total of 18 parameters found to be significant from the author's previously published literature were short-listed. Each parameter was given a score ranging from 0 to 2, with a minimum total score of 1 and a maximum total score of 26. Risk stratification of EPN was done based on a combined prognostic score. Those with a score of 1–8 were grouped under the very low-risk category. The low-risk group scored 9–15, the intermediate-risk group scored 16–20, and those with a score of > 20 (high-risk group) carried a much higher risk of succumbing to the disease. The maximum score that could be obtained was 26 (read authors' earlier publication for reference)[4].

The NEWS 2 is a scoring system based on a simple aggregate of six physiological parameters routinely measured and monitored in emergency rooms. The parameters studied are respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of Consciousness and body temperature. Each of the six parameters is assigned a score that reflects the extremes of variability from the standard set norm. The higher the score, the greater the variability from the standard norms. The maximum cumulative score is 20. The NEWS 2 score was then calculated for each admitted patient and classified into three groups. Traditionally, the aggregate score of 5 and above is a critical threshold value that triggers the need for an urgent clinical assessment and review. A score of 7 and above triggers the need for an elevated clinical response, necessitating an emergency clinical review.

While the NEWS 2 score perfectly holds good for the initial triaging, an initial pilot study on treatment outcomes revealed considerable overlap between the scores. Treatment outcomes in patients with scores of 5 and 6 behaved almost the same as those between 0 and 4. Similarly, patients with scores between 7 and 14 behaved very differently from those with a score of 15 and above. This prompted us to revisit the NEWS 2 score and see if this score can be modified only regarding treatment outcomes.

A weighted average risk stratification index was calculated for the three groups. The weighted average is the average of a data set that ensures similar data points are equal in the proportion represented. The weighted average is calculated by multiplying each value in the set by its weight, then adding up the products and calculating its average. The weighted average risk stratification index was calculated as follows: For example, 20 patients in group 1, with 2 patients, 4 patients, 6 patients and 8 patients having a risk stratification index of 1, 2, 3 and 4, respectively. In that case, the weighted average

is calculated as follows: (2 × 1) + (4 × 2) + (6 × 3) + (8 × 4) divided by 20, 2 + 8 + 18 + 32 divided by 20, which means 60 ÷ 20 = 3. This group's Weighted average Risk stratification index would be measured as 3. This formed the basis for modifying the NEWS 2 scoring system.

The scores of 5 and 6 were combined with 0 to 4 and were included in group 1. Scores of 7 to 20 were divided into two groups. Group 2 included patients with scores of 7 to 14. Patients with scores of 15 and above were included in group 3. All the qualitative and quantitative variables between the revised three groups were analyzed and compared with treatment outcomes. All patients were divided into three broad groups: (1) Group 1; (2) Group 2; and (3) Group 3.

A preliminary calculation was done based on the original NEWS 2 score (Table 1). We observed that the weighted average risk stratification index between the three groups was significant, but when rounded off to the nearest whole number, it was the same for all three groups. Table 1 was formulated by dividing group 3 into two groups (7-14 and 15-20). In Table 1, the group 3 was subdivided into three subgroups (7-10, 11-14 and 15-20). In Table 1, groups 1 and 2 behaved alike. Table 1 combined groups 1 and 2 and subdivided group 3 into two subgroups (7-14 and 15-20). Though the need for intervention was almost the same in groups 1 and 2, mortality was noted only in group 2. Table 1 was finally considered to be the mNEWS 2 score.

Figure 1 gives a graphic representation of the distribution of the risk stratification indices across various NEWS 2 groups. The standard NEWS 2 groups (0-4, 5-6 and 7-20) matched the mNEWS 2 scores of 0-6, 7-14 and 15-20. The groups 0-4 and 0-6 almost behaved the same. Groups 5-6 and 7-14 behaved virtually the same, except that significant numbers with higher risk stratification would have missed out if the original scoring was considered. Similarly, the modified group 3 includes only patients with a higher risk index, so focused treatment could be offered to the smaller group of patients who deserve it more.

Also, the sensitivity, specificity, positive and negative predictive value (NPV) and accuracy of the testing were calculated (see Table 2 for reference). The sensitivity and accuracy rates were maximal for the NEWS 2 score cutoff value of 15 and above, which formed the basis for the mNEWS 2 scoring.

Figure 2 shows the NEWs 2 scores on the X axis and the percentage of sensitivity (green line) and specificity (red line) on the Y axis. The sensitivity and specificity are maximal for a score of 15 and above. Hence, the cutoff value of 15 and above is chosen to include patients in group 3.

The selection of specific cutoff values for the mNEWS 2 score was based on clinical observations, statistical modelling, and predictive performance analysis. An initial pilot study revealed overlapping treatment outcomes in specific score ranges, particularly between scores 5–6 and 0–4, and among patients scoring 7–14 compared to those scoring ≥ 15. We employed weighted average risk stratification indices to refine risk stratification, ensuring that each group had distinct clinical outcomes.

Further justification for these cutoffs comes from sensitivity, specificity, and accuracy calculations, which identified a threshold at a NEWS 2 score of 15, where predictive performance was maximized. This was validated through receiver operating characteristic (ROC) curve analysis, confirming that the new stratification better aligns with intervention needs and mortality risk. While this modification improves outcome differentiation within our cohort, we acknowledge the need for external validation in diverse clinical settings to confirm its broader applicability.

The mNEWS 2 score was designed to retain the simplicity and ease of application of the original NEWS 2 system. The reclassification groups align with clinically relevant risk stratification while maintaining an intuitive scoring structure that can be seamlessly used in emergency settings without additional complexity.

Statistical analysis

The collected data were entered into Microsoft Excel 2016 and analyzed using Statistical Package for the Social Sciences, version 19. Descriptive statistics were used to summarize the characteristics of the sample: Continuous variables were presented as mean and SD, while categorical variables were reported as frequencies and percentages. For inferential analysis, analysis of variance with post hoc multiple comparisons was used to compare continuous variables across more than two groups. The χ^2 test was applied to analyze categorical variables. An independent sample *t*-test assessed significant differences between the two groups. To determine the optimal cutoff score, ROC curve analysis was performed, and sensitivity, specificity, positive predictive value, and NPV were calculated. A significance level of 5% ($P < 0.05$) was considered statistically significant.

RESULTS

A total of 171 patients with EPN were included in our study. Table 3 illustrates the demographic data of patients in our study. Females were more commonly involved in all three groups. While fever was common in all three groups, temperature extremes were observed more commonly in groups 2 and 3. Most patients in groups 1 and 2 were alert, conscious, and oriented to time, place, and person. Only one-third in group 3 were alert.

Diabetes mellitus was a common occurrence in all three groups. A palpable tender kidney was seen in all patients with a NEWS 2 score of above 15 and nearly two-thirds with a score of 7 to 14. Similarly, hemodynamic instability, shock at initial Presentation, and the need for intensive monitoring and Hemodialysis were observed in high numbers in patients with a score of 15 and above. The mean combined prognostic scoring was found to correlate directly with the NEWS 2 score. A higher prognostic score was observed in patients with higher NEWS 2 scores ($P < 0.01$). Similarly, most patients in groups 1 and 2 had a lower while three-fourths of patients in group 3 had a higher risk stratification index of 4 ($P < 0.01$).

Table 1 Grouping of patients based on original National Early Warning Score 2 and its various modifications, *n* (%)

Original NEWS 2 score						
Weighted average risk stratification index	Group 1: Score 0-4 (n = 48)	Group 2: Score 5 and 6 (n = 35)	Group 3: Scores 7-20 (n = 88)			P value
	1.875	1.857	2.44			0.02
Risk stratification index (rounded off)	2	2	2			
Need for intervention	33 (68.75)	27 (77.14)	71 (80.68)			< 0.01
Mortality	0	0	8			< 0.01
Group 3, subdivided into two						
Weighted average risk stratification index	Group 1: Score 0-4 (n = 48)	Group 2: Score 5 and 6 (n = 35)	Group 3: Scores 7-20 (n = 88)			P value
			Scores 7-14 (n = 76)	Scores 15-20 (n = 12)		
	1.875	1.857	2.319	3.75		< 0.01
Risk stratification index (rounded off)	2	2	2	3		
Need for intervention	40 (83.33)	27 (77.14)	61 (80.26)	12 (100)		< 0.01
Mortality	0	0	1	7		< 0.01
Group 3, subdivided into three						
Risk stratification	Group 1: Score 0-4 (n = 48)	Group 2: Score 5 and 6 (n = 35)	Group 3: Scores 7-10 (n = 55)	Group 4: Scores 11-14 (n = 21)	Group 5: Scores 15-20 (n = 12)	P value
Weighted average risk stratification index	1.875	1.857	1.982	2.762	3.75	< 0.01
Weighted average risk stratification index (rounded off)	2	2	2	3	4	
Need for intervention	40 (83.33)	27 (77.14)	44 (80)	17 (80.95)	12 (100)	< 0.01
mortality	0	0	0	1	7	< 0.01
Modified NEWS 2 scoring system						
Parameters	Group 1: Score 0-6 (n = 83)	Group 2: Score 7-14: n = 76	Group 3: Score 15-20 (n = 12)			P value
Weighted average Risk stratification index	1.867	2.039	3.75			< 0.01
Risk stratification index (rounded off)	2	2	4			
Need for intervention	67 (80.72)	60 (78.95)	12 (100)			< 0.01
mortality	0	1 (1.32)	7 (58.33)			< 0.01

NEWS 2: National Early Warning Score 2.

The demographic variables like patient age, sex, laterality, body mass index, the six parameters of NEWS 2 score, hemodynamic stability, comorbidities and need for intensive care monitoring were tabulated for each of the three groups (Table 3).

Across all groups, females were more commonly affected, with a higher female-to-male ratio observed in groups 2 and 3. Advanced age correlated with increasing severity, as all patients in group 3 were above 50 (P = 0.046). Fever was a common presenting symptom in all groups, but extreme temperature variations (< 36.8 °C or > 40 °C) were significantly more frequent in group 3 (58.3%) compared to groups 1 and 2 (P < 0.01). Similarly, altered mental status was more prevalent in patients with higher NEWS 2 scores, with only one-third of group 3 remaining alert at Presentation (P < 0.01).

Hemodynamic instability was a key distinguishing factor among the groups. While nearly all patients in group 1 were stable at presentation, 91.67% of group 3 presented with shock (P < 0.01). A palpable, tender kidney was universally noted in group 3, correlating with increased disease severity (P < 0.01). The need for intensive care monitoring and hemodialysis was also significantly greater in group 3, highlighting the critical condition of this subset.

Table 2 Cutoff National Early Warning Score 2 for mortality

Cutoff National Early Warning Score 2 for mortality	Sensitivity % (95%CI)	Specificity % (95%CI)	Positive predictive value % (95%CI)	Negative predictive value % (95%CI)	Accuracy % (95%CI)
≥ 7	100 (63.06-100)	50.92 (42.98-58.82)	9.09 (7.88-10.47)	100 (95.65-100)	53.22 (45.45-60.87)
≥ 8	100 (63.06-100)	58.90 (50.93-66.53)	10.67 (9.04-12.55)	100 (96.23-100)	60.82 (53.07-68.18)
≥ 9	100 (63.06-100)	69.94 (62.27-76.86)	14 (11.44-17.10)	100 (96.82-100)	71.35 (63.94-77.99)
≥ 10	100 (63.06-100)	80.98 (74.10-86.7)	20.51 (15.82-26.16)	100 (97.24-100)	81.87 (75.27-87.34)
≥ 11	100 (63.06-100)	84.66 (78.20-89.82)	25.24 (18.24-31.46)	100 (97.36-100)	85.38 (79.18-90.31)
≥ 12	100 (63.06-100)	86.50 (80.28-91.34)	26.67 (19.78-34.91)	100 (97.42-100)	87.13 (81.17-91.76)
≥ 13	100 (63.06-100)	89.57 (83.83-93.81)	32 (23.08-42.46)	100 (97.51-100)	90.06 (84.56-94.10)
≥ 14	100 (63.06-100)	91.41 (86.01-95.22)	36.36 (25.72-48.53)	100 (97.55-100)	91.81 (86.64-95.45)
≥ 15	87.50 (47.35-99.68)	96.93 (92.99-99)	58.33 (36.23-77.53)	99.37 (96.19-99.9)	96.49 (92.52-98.70)
≥ 16	75 (34.91-96.81)	98.16 (94.72-99.62)	66.67 (37.82-86.8)	98.77 (96.01-99.63)	97.08 (93.31-99.04)
≥ 17	50 (15.7-84.3)	98.77 (95.64-99.85)	66.67 (29.97-90.34)	97.58 (95.27-98.77)	96.49 (92.52-98.7)
≥ 18	25 (3.19-65.09)	100 (97.76-100)	100 (15.81-100)	96.45 (94.79-97.59)	96.49 (92.52-98.7)
≥ 19	12.50 (0.32-52.65)	100 (97.76-100)	100 (2.50-100)	95.88 (94.71-96.8)	95.91 (91.75-98.34)

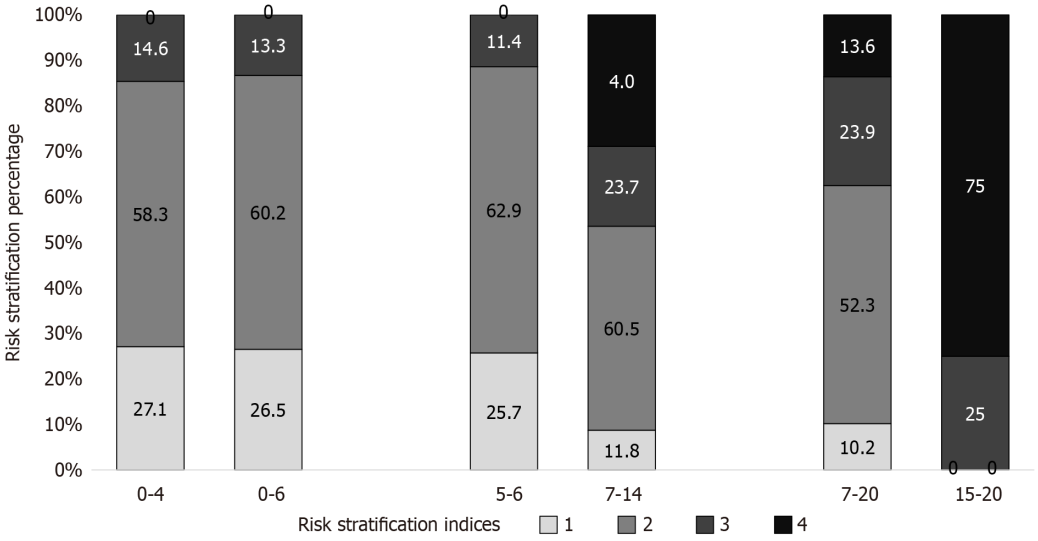

Figure 1 Comparison of the risk stratification indices with the National Early Warning Score 2 and modified National Early Warning Score 2.

Table 4 illustrates the details of various biochemical parameters and radiological variables in three groups. The mean blood sugar and hemoglobin A1c (HbA1c) levels were significantly higher in group 3. All other blood biochemistry (except leukocyte count) showed a significant difference between group 3 and other groups. The computed tomography (CT) scan of all patients in group 3 had a class 3 or 4 EPN, while most in groups 1 and 2 had class 1 and 2 EPN.

Biochemical parameters further supported the stratification of disease severity. Group 3 had markedly elevated blood glucose levels (mean 346.16 mg/dL) and HbA1c levels (10.07%), reinforcing the strong association between diabetes and severe EPN (P = 0.023). Similarly, renal function markers such as serum creatinine were significantly elevated in group 3 (mean 5.14 mg/dL, P = 0.003), suggesting a higher likelihood of acute kidney injury in this cohort. Hypoalbuminemia and hyponatremia were also pronounced in group 3, further emphasizing the impact of systemic inflammation and metabolic derangements in disease progression.

Radiologically, CT findings correlated well with clinical severity. Patients in groups 1 and 2 predominantly had class 1 and 2 EPN, whereas all patients in group 3 exhibited class 3 or 4 disease, indicating widespread parenchymal involvement and increased risk of complications (P < 0.01).

Table 5 gives details of the treatment given to our patients. All 32 patients (100%) who were medically treated and conservatively managed were from group 1. Six patients in group 3 had a double J stenting done. The remaining six (in group 3) either had an early nephrectomy (n = 4) or succumbed to the illness (n = 2). Early nephrectomy was performed

Table 3 Demographic data of emphysematous pyelonephritis patients in our study, *n* (%)

Pt characteristics	Group 1: Score 0-6 (*n* = 83)	Group 2: Score 7-14 (*n* = 76)	Group 3: Score 15-20 (*n* = 12)	*P* value
Mean age in years (SD)	52.639 (10.55)	55.553 (11.95)	60.083 (3.45)	0.046
Age > 50 years				0.053
Yes	56 (67.47)	57 (75)	12 (100)	
No	27 (32.53)	19 (25)	0	
Sex				
Male	39 (46.99)	25 (32.90)	5 (41.67)	0.194
Female	44 (53.01)	51 (67.10)	7 (58.33)	
Sex (female:male)	1.1:1	2.1:1	1.4:1	
Laterality				0.162
Unilateral	68 (81.93)	70 (92.10)	10 (83.33)	
Bilateral	15 (18.07)	6 (7.90)	2 (16.67)	
Body temp				< 0.01
No fever	29 (34.94)	11 (14.47)	0 (0)	
Temp between 37-40 °C	54 (65.06)	58 (76.31)	5 (41.67)	
Temp < 36.8 °C, > 40 °C	0	7 (9.21)	7 (58.33)	
Level of consciousness				< 0.01
Alert	82 (98.8)	51 (67.10)	4 (33.33)	
Disoriented/unconscious	1 (1.2)	25 (32.90)	8 (66.67)	
Other parameters				
Palpable tender kidney	7 (8.43)	48 (63.16)	12 (100)	< 0.01
Shock at presentation	1 (1.21)	20 (2.63)	11 (91.67)	< 0.01
Need for intensive care unit care	9 (10.84)	43 (56.58)	12 (100)	< 0.01
Need for hemodialysis	5 (5.95)	15 (19.74)	11 (91.67)	< 0.01
Presence of diabetes mellitus	71 (85.6)	73 (96.1)	12 (100)	0.035
Early nephrectomy	0 (0)	2 (2.63)	6 (50)	< 0.01
Mean combined prognostic scoring (SD)	10.74 (3.81)	12.95 (3.90)	21.92 (2.61)	< 0.01
Risk stratification index				< 0.01
1	22 (26.5)	9 (11.84)	0	
2	50 (60.24)	46 (60.52)	0	
3	11 (13.25)	18 (23.68)	3 (25)	
4	0 (0)	3 (3.95)	9 (75)	

in 8 patients, of which two patients died after surgery. However, all four patients in group 3, who had an early nephrectomy done, recovered well after surgery. Ten patients in group 3 had either PCN or percutaneous catheter drainage (PCD) placed or both. Seven out of 8 mortality (87.5%) were observed in group 3 patients.

Treatment strategies and outcomes varied significantly between groups. Non-surgical management was effective in all 32 patients from group 1, while interventional procedures such as PCD and PCN were increasingly required in groups 2 and 3. Notably, 50% of patients in group 3 underwent early nephrectomy, reflecting the aggressive nature of the disease in this subset ($P < 0.01$).

The mortality rate was disproportionately high in group 3, with 7 out of 12 patients (58.3%) succumbing to the illness, compared to just one patient (1.3%) in group 2 and none in group 1 ($P < 0.01$). The NEWS 2 score was found to be a strong predictor of mortality, with a cutoff of ≥ 15 demonstrating the highest predictive accuracy (96.49%), emphasizing its utility as a clinical decision-making tool.

Table 2 summarizes the sensitivity and specificity for mortality at various cutoff NEWS 2 scores from 7 to 18. The cutoff score of ≥ 15 showed the highest accuracy report of 96.49. The specificity, positive and negative predictive values were also maximum at this cutoff value of ≥ 15. This formed the basis for redefining the NEWS 2 scores regarding treatment-

Table 4 Biochemical and radiological variables, *n* (%)

Biochemical variables	Group 1: Score 0-6 (*n* = 83)	Group 2: Score 7-14 (*n* = 76)	Group 3: Score 15-20 (*n* = 12)	*P* value
Absolute leukocyte count (SD)	15394.2 (6895.11)	16489.3 (7478.58)	20778.3 (7875.63)	0.152
Heart rate (per minute) (SD)	86.711 (12.58)	90.026 (17.79)	110.750 (21.16)	< 0.01
Blood sugar on admission (mg/dL) (SD)	245.578 (100.78)	323.21 (129.33)	346.167 (59.12)	< 0.01
Hemoglobin A1c (SD)	8.712 (2.55)	9.375 (1.7)	10.07 (2.59)	0.023
S creatinine on admission (mg/dL) (SD)	3.187 (2.21)	3.928 (2.54)	5.14 (1.45)	0.003
International normalized ratio test (SD)	1.18 (0.18)	1.27 (0.31)	1.86 (0.61)	< 0.01
Serum sodium level (mEq/L) (SD)	131.94 (6.03)	131.90 (5.76)	123.58 (4.89)	< 0.01
Serum albumin (grams/dL) (SD)	3.14 (0.65)	3.08 (0.73)	2.392 (0.45)	0.004
Platelet count (SD)	220695.181 (128292.52)	124053.947 (87178.32)	54575.000 (25853.30)	< 0.01
Mean hospital stay (days) (SD)	5.7 (2.99)	7.6 (3.72)	8.3 (4.72)	< 0.01
Computed tomography classification				< 0.01
Class 1	32 (38.55)	11 (14.47)	0 (0)	
Class 2	25 (30.12)	33 (43.42)	0 (0)	
Class 3A	9 (10.84)	9 (11.82)	1 (8.33)	
Class 3B	2 (2.41)	15 (19.74)	2 (2.63)	
Class 4	15 (18.07)	8 (10.53)	9 (11.84)	

Table 5 Summary of treatment given to our patients, *n* (%)

Treatment given	Group 1: Score 0-6 (*n* = 83)	Group 2: Score 7-14 (*n* = 76)	Group 3: Score 15-20 (*n* = 12)	*P* value
Non-surgical treatment (*n* = 32)	32 (100)	0 (0)	0 (0)	< 0.01
DJ stenting (*n* = 127)	49 (59)	72 (94.7)	6 (50)	< 0.01
Percutaneous nephrostomy (*n* = 26)	4 (4.8)	14 (18.4)	8 (66.7)	< 0.01
Percutaneous catheter drainage (*n* = 28)	5 (6)	16 (21.1)	7 (58.3)	< 0.01
Need for hemodialysis (*n* = 31)	5 (6)	15 (19.7)	11 (91.7)	< 0.01
Early nephrectomy (*n* = 8)	0 (0)	2 (2.6)	6 (50)	< 0.01
Mortality (*n* = 8)	0 (0)	1 (1.3)	7 (58.3)	< 0.01

related outcomes.

The ROC curve gives us a visual and graphic illustration of the study's performance across various thresholds. In this graph, we plotted the false positive rates on the X-axis and true positive values on the Y-axis. The area under the curve (AUC) measures the performance of the model under study.

Although this table reiterates data from Tables 2, 3, 4, and 5, it highlights the most clinically relevant differences across groups. Group 3 (mNEWS 2: 15-20) consists entirely of patients over 50 years, compared to 67.5% in group 1 (mNEWS 2: 0-6). Body temperature extremes, shock at presentation, and altered consciousness increased significantly across the groups, with shock affecting 91.7% and altered consciousness in 66.7% of group 3 patients. A palpable tender kidney, present in 100% of group 3 patients, is a key distinguishing clinical feature (Table 6).

The need for ICU care, haemodialysis, and early nephrectomy rises sharply, with ICU admission required for all group 3 patients and 50% undergoing nephrectomy. Absent in group 1, mortality reaches 58.3% in group 3, emphasizing the prognostic significance of disease severity.

Laboratory markers reflect worsening systemic dysfunction. Heart rate, mean blood sugar, and serum creatinine increase significantly while serum albumin and platelet count decline, suggesting progressive metabolic and hematologic deterioration. International normalized ratio test rises in group 3, indicating a higher bleeding risk. CT class 3/4 findings, seen in all group 3 patients, confirm the radiologic progression of the disease. Statistically significant differences ($P < 0.01$ for most parameters) underscore the mNEWS 2 score's predictive value in identifying critically ill patients, guiding clinical decision-making, and stratifying risk effectively.

It summarizes the progressive worsening of clinical parameters with increasing mNEWS 2 scores, highlighting significant differences in disease severity, organ dysfunction, and mortality.

Table 6 Summary of key clinical differences among emphysematous pyelonephritis groups

Clinical parameter	Group 1 (NEWS 2: 0-6, *n* = 83)	Group 2 (NEWS 2: 7-14, *n* = 76)	Group 3 (NEWS 2: 15-20, *n* = 12)	*P* value
	Percentage (95%CI)/mean ± SD (95%CI)			
Age > 50 years (%)	67.50 (58.9-75.4)	75 (65.4-82.8)	100 (73.5-100)	0.046
Body temperature extremes (%)	0 (0-4.4)	9.21 (4.5-17.8)	58.30 (34.8-78.4)	< 0.01
Shock at presentation (%)	1.20 (0.2-6.5)	26.30 (18.2-36.1)	91.70 (65.3-98.8)	< 0.01
Altered consciousness (%)	1.20 (0.2-6.5)	32.90 (24.2-42.9)	66.70 (41.0-85.6)	< 0.01
Palpable tender kidney (%)	8.40 (4.1-16.3)	63.20 (52.4-72.9)	100 (73.5-100)	< 0.01
Presence of diabetes mellitus (%)	85.6 (76.1-92)	96.1 (88.9-99.18)	100 (73.5-100)	0.035
Need for intensive care unit care (%)	10.80 (6.0-18.6)	56.60% (45.7-66.9)	100 (73.5-100)	< 0.01
Need for hemodialysis (%)	6.00 (2.7-12.7)	19.70% (12.7-29.2)	91.70 (65.3-98.8)	< 0.01
Early nephrectomy (%)	0 (0-4.4)	2.60 (0.7-9.0)	50 (26.9-73.1)	< 0.01
Mortality (%)	0 (0-4.4)	1.30 (0.2-6.9)	58.30 (34.8-78.4)	< 0.01
Heart rate (per minute)	86.71 ± 12.58 (84.004- 89.416)	90.03 ± 17.79 (86.03-94.03)	110.75 ± 21.16 (98.78-122.72)	< 0.01
Mean blood sugar (mg/dL)	245.6 ± 100.8 (225.4-265.8)	323.2 ± 129.3 (298.5-347.9)	346.2 ± 59.1 (325.4-367.0)	< 0.01
Serum creatinine (mg/dL)	3.18 ± 2.21 (2.7-3.6)	3.92 ± 2.54 (3.3-4.5)	5.14 ± 1.45 (4.6-5.7)	0.003
Serum albumin (g/dL)	3.14 ± 0.65 (2.9-3.3)	3.08 ± 0.73 (2.9-3.3)	2.39 ± 0.45 (2.2-2.6)	0.004
Hemoglobin A1c	8.712 ± 2.55 (8.16- 9.26)	9.375 ± 1.7 (8.99-9.76)	10.07 ± 2.59 (8.665-11.53)	0.023
Sodium (mEq/L)	131.94 ± 6.03 (130.3-133.6)	131.90 ± 5.76 (130.3-133.4)	123.58 ± 4.89 (121.4-125.8)	< 0.01
International normalized ratio test	1.18 ± 0.18 (1.14- 1.22)	1.27 ± 0.31 (1.2- 1.34)	1.86 ± 0.61 (1.515-2.205)	< 0.01
Platelet count	220695 ± 128292 (189345-252045)	124053 ± 87178 (101345-146761)	54575 ± 25853 (45676-63474)	< 0.01
Computed tomography class 3/4 (%)	20.50 (13.6-29.6)	30.30 (21.5-40.4)	100% (73.5-100)	< 0.01
Risk stratification index (mean ± SD)	1.867 ± 0.35 (1.8-2.0)	2.039 ± 0.45 (1.9-2.2)	3.75 ± 0.50 (3.5-4.0)	< 0.01
Combined prognostic scoring index (mean ± SD)	10.74 ± 3.81 (9.8-11.7)	12.95 ± 3.90 (11.9-14.0)	21.92 ± 2.61 (20.9-23.0)	< 0.01

NEWS 2: National Early Warning Score 2.

Figure 3 illustrates our study's ROC curve. The true positive rates and false positive values for the NEWS 2 scores ranging from 1 to 20 were plotted in the Y and X axes, respectively. The AUC was then measured. The AUC to predict the mortality based on the News 2 score is 0.984 with a confidence interval of (0.966, 1) (*P* value < 0.001). This suggests that the cutoff value of 15 and above most specifically correlates with the degree of mortality.

Clinical implications

The findings of this study underscore the prognostic significance of the NEWS 2 score in EPN patients. Higher scores correlate with increased mortality, greater need for intensive care, and more invasive interventions. The strong association between biochemical markers, hemodynamic instability, and disease severity highlights the importance of early risk stratification. These results reinforce the necessity of timely intervention in high-risk patients, with aggressive management strategies potentially improving outcomes in those with severe disease.

DISCUSSION

The last two decades have witnessed a paradigm shift in evaluating and managing urological emergencies. With abundant e-resources available and the curiosity and keenness to know about their problems increasing many folds amongst the patients seeking treatment, predicting risk has become an essential and integral component of medical/surgical care. Prognostic scoring systems are formulated, risk stratification indices are developed, and nomograms and guidelines are established for each urological condition to facilitate the prognostication and treatment of various urological diseases and emergencies.

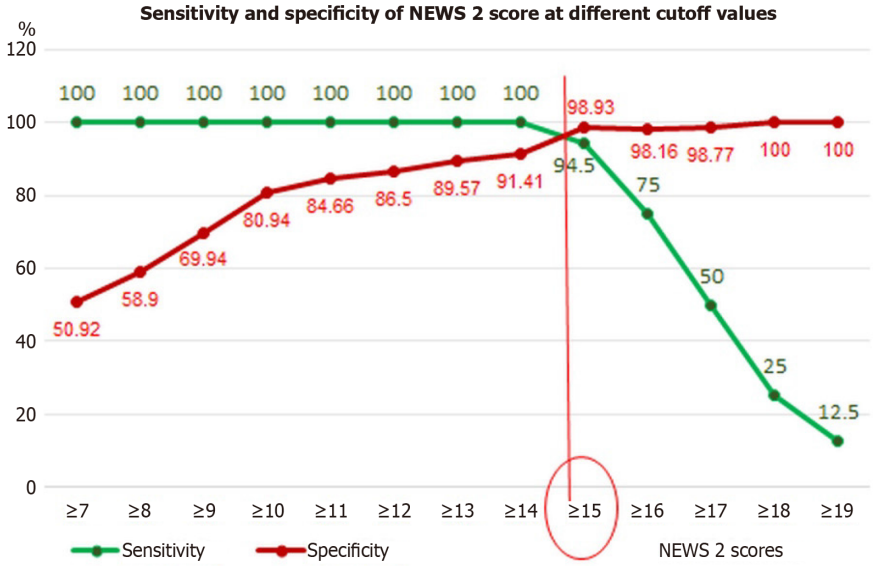

Figure 2 Sensitivity and specificity of National Early Warning Score 2 at various cutoff values. NEWS 2: National Early Warning Score 2.

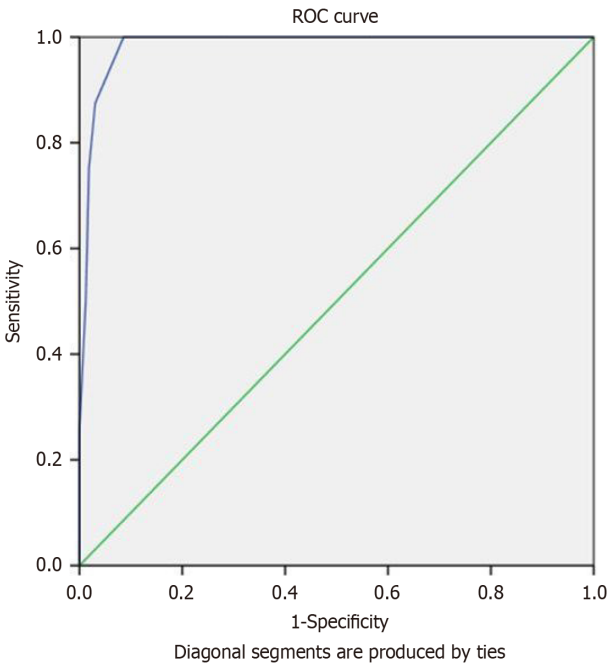

Figure 3 Receiver operating characteristic curve for predicting mortality according to modified National Early Warning Score 2 score. ROC: Receiver operating characteristic.

Various authors have studied the role of such predictive scores in the management of renal stone diseases, planning partial nephrectomy in solid renal masses and nomograms for prostate cancer[24-27]. Machine learning methods are being used these days to assess the predictability of the success of a surgical procedure[28]. Integrating machine learning techniques could further enhance the predictive accuracy and clinical applicability of the mNEWS 2 score. Machine learning models, such as logistic regression, random forests, or neural networks, could analyze large datasets to refine risk stratification by identifying complex interactions between clinical parameters. Such an approach may enable dynamic score adjustments, improving early detection of high-risk patients and optimizing triage decisions. Future research should focus on developing and validating machine learning-driven models that complement the mNEWS 2 score while ensuring interpretability and ease of integration into clinical workflows.

NEWS 2 scoring system is one such standardized and systematized early warning system that has been validated and extensively used in the United Kingdom and the rest of European countries. It greatly aids the activation of the hospital's rapid response teams on time[29]. The main application of this scoring system has been in the emergency room, where triaging of patients who need more intensive monitoring/stabilization is done based on various physiological parameters.

Multiple studies have looked into the various predictive scores for EPN. Chawla *et al*[30] compared various predictive scores that facilitated expedited care in EPN patients. Kim *et al*[31] studied the role of blood culture and axial imaging in assessing the clinical utility for diagnosing pyelonephritis and predicting hospital mortality. Elbaset *et al*[32] studied the role of platelet-to-leukocyte ratio as a marker of sepsis in EPN patients. Bedoui *et al*[33] identified absolute leukocytic and lymphocytic counts at admission as independent predictors of urosepsis in EPN patients. MEWS 2, quick SOFA, SOFA and SIRS score have been extensively studied. The NEWS 2 score is the best predictor of the need for expedited ICU care [34]. However, when we correlated risk stratification with the NEWS 2 score, we observed that the rounded-off risk score was the same across all three NEWS 2 groups. Group 3 patients, with a score of 7 to 20, had a considerable overlap with patients in group 2 (score of 5 and 6). Similarly, scores 5 and 6 overlapped considerably with scores 0-4. The cutoff score for mortality with the highest degree of accuracy and sensitivity, specificity, and predictive values was 15. Hence, the mNEWS 2 score (0-6, 7-14 and 15-20) was used to assess the various treatment outcomes. This is the first-ever study on urological emergencies using the mNEWS 2 scoring system.

Our study had a female preponderance, with most patients aged 50 years and above. Diabetes mellitus is the most commonly associated comorbidity in such patients. Yap *et al*[35] observed diabetes in 90% of their EPN patients. Our study highlights a significant association between diabetes mellitus and EPN severity, with its prevalence increasing across severity groups ($P = 0.035$) (Table 3). Additionally, higher blood sugar and HbA1c levels were observed in patients with worse clinical outcomes ($P < 0.01$ and $P = 0.023$, respectively) (Table 4). Diabetes is known to impair immune function through mechanisms such as reduced neutrophil activity, microvascular dysfunction, and hyperglycemia-induced bacterial proliferation, all of which may contribute to more severe disease progression. While our results emphasize the role of diabetes, other comorbidities, such as chronic kidney disease and hypertension, may also influence outcomes. Further studies with multivariate analysis could help delineate the independent impact of diabetes on disease severity. These findings have important clinical implications, suggesting that glycemic control may play a role in risk stratification and treatment planning for EPN patients. Integrating diabetes status with prognostic scoring systems like NEWS 2 could enhance the early identification of high-risk individuals and guide more aggressive management strategies. While our study provides substantial evidence of an association, future prospective studies should evaluate whether targeted glycemic control can improve outcomes in this patient population.

A palpable tender kidney is one of the sure clinical signs associated with a higher mNEWS 2 score. All patients in group 3 and two-thirds in group 2 had a palpable tender kidney. Also, all eight early nephrectomies had a palpable tender kidney, while all eight who succumbed to this illness also had a palpable tender kidney. No other authors have correlated the significance of palpable kidneys to the ultimate treatment outcomes.

Trujillo *et al*[36] proposed a risk assessment score that predicted treatment outcomes in patients with EPN. In the largest-ever multi-centric study on EPN involving 570 patients from 15 centres, they proposed an 8-point scoring system to predict mortality in EPN[36]. They predicted a 100% mortality for a score of 7. In our study, two-thirds of our patients (66.67%) with a prognostic score of 22 and above succumbed to the illness.

Thrombocytopenia, chronic kidney disease, and hyponatremia at presentation were found to be associated with high mortality[37,38]. Our study also observed these biochemical parameters were significantly associated with higher mortality. Falagas *et al*[39], in their meta-analysis of 175 patients from 7 published studies, observed an overall mortality of 25%. They observed that mortality was associated with thrombocytopenia, conservative treatment, and bilaterality. Our study also noted these parameters closely correlating with higher mNEWS 2 scores.

To our knowledge, this is the first-ever and the largest single-centre study that compared the subgroups of group 3 of the NEWS 2 score. Our study stresses the need to implement mNEWS 2 scores in managing EPN patients. While the NEWS 2 score is a standardized system for triaging patients who need intensive monitoring, the conventional scoring exhibits a considerable overlap between the three groups. This necessitates and reinforces the growing need to modify the NEWS 2 score, which would greatly help the urologists prognosticate the treatment outcomes.

The revised scoring system can be easily incorporated into existing electronic medical record (EMR) systems, automated triage software, or bedside calculation tools, ensuring its practical implementation in emergency care. By improving the accuracy of risk stratification, mNEWS 2 enhances clinical decision-making without disrupting workflow efficiency. The mNEWS 2 score maintains the same core physiological parameters as the NEWS 2 system to ensure real-time usability. The reclassification does not require additional measurements or manual recalculations, allowing for rapid risk assessment at the point of care.

Bias and limitations

Our study provides valuable insights into the prognostic significance of NEWS 2 scores in EPN; however, certain limitations must be acknowledged.

The 12-year data collection period includes cases before the introduction of NEWS 2 in 2017, which may introduce inconsistencies, though standardized medical records ensured uniform data collection.

Variability in clinical management among multiple urologists could have influenced outcomes, but this reflects real-world practice, enhancing generalizability.

Demographic attributes such as origin, ethnicity, or language were not analyzed, as the focus was on clinical parameters and prognostic scoring in EPN. Future research incorporating demographic variations may provide further insights into population-specific disease patterns and management.

The small sample size of group 3 ($n = 12$) may limit subgroup analysis, though it aligns with the natural incidence of severe cases.

The study's single-centre design restricts external validity and ensures consistent data collection and standardized protocols. The lack of external validation is another limitation, emphasizing the need for a prospective multi-centre study to further substantiate findings, compare mNEWS 2 scores with other scoring systems, and assess the clinical applic-

ability of mNEWS 2 in diverse populations.

Information bias from over-reliance on medical records and potential confounding factors such as prior treatments and pre-existing conditions may have influenced outcomes.

Lack of prospective validation is another limitation. It restricts the ability to fully assess the mNEWS 2 score's predictive accuracy compared to other established scoring systems. Future studies would focus on validating the score in larger, independent cohorts to strengthen its prognostic reliability.

Future directions

To further improve global patient care for EPN, we propose integrating mNEWS 2 into EMR and clinical decision support systems for real-time triage and early intervention. Multi-centre validation studies and a global EPN registry could enhance risk prediction and treatment protocols. Machine learning models could further refine risk stratification, enabling personalized treatment pathways. Expanding telemedicine and remote monitoring can improve post-discharge follow-ups and early detection of complications. Finally, developing internationally standardized EPN management guidelines will ensure consistent, evidence-based treatment worldwide. These advancements will help reduce morbidity and mortality and optimize critical care decisions globally.

CONCLUSION

While the NEWS 2 score is an established scoring system for the initial triaging of patients with EPN, our study reiterates the need for a mNEWS 2 scoring to facilitate an appropriate assessment of treatment-related outcomes. A prompt diagnosis, early risk assessment, and proper treatment strategies based on the mNEWS 2 score would further reduce morbidity and mortality in patients with EPN. Our study introduces the mNEWS 2 score, a refined risk stratification tool for EPN, improving the predictive accuracy of the original NEWS 2 system. By reassessing cutoff thresholds, mNEWS 2 better correlates with disease severity, treatment outcomes, and mortality risk, enhancing clinical decision-making in urological emergencies. The mNEWS 2 scores should be seamlessly implemented into EMR, aiding real-time triage and patient management.

FOOTNOTES

Author contributions: Krishnamoorthy S played a major role in the study by conceiving the idea, designing the research framework, and writing the full manuscript; Thiruvengadam G performed the statistical analysis, contributed to manuscript writing, and played a key role in the study's execution; Sekar H, Palaniyandi V, Ramadurai S, and Narayanasamy S were responsible for data collection and management of patients; all authors reviewed, revised, and approved the final manuscript.

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Informed consent statement: Informed consent was not required for this study as it is a prospective analysis utilizing anonymized patient data from medical records, with no direct patient interaction or intervention. The study was conducted in accordance with institutional ethical guidelines and regulatory standards for observational research, ensuring patient confidentiality and data protection.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

Data sharing statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and institutional regulations, access to patient-specific data is restricted to ensure confidentiality and compliance with data protection policies.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Radial artery deviation and reimplantation technique *vs* classical technique in arterio-venous fistula: A randomised control trial

Shakti S Sarangi, Shashank Kumar, Deepak P Bhirud, Mahendra Singh, Shiv C Navriya, Gautam Ram Choudhary, Arjun Singh Sandhu

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Abstract

BACKGROUND

Surgically created arterio-venous fistulas (AVFs) are the gold standard for haemodialysis access for patients with end-stage renal disease. Standard practice of AVF creation involves selecting the non-dominant upper limb and starting with most distally with radio-cephalic arterio-venous fistula. The primary patency rate of radio-cephalic arterio-venous fistula varies from 20%-25%. It has been suggested the neointimal hyperplasia at the mobilized venous segment causes stenosis of the anastomosis. Therefore, the radial artery deviation and reimplantation (RADAR) technique, in which the vein is minimally mobilized, should result in a higher success rate.

AIM

To compare the RADAR technique with classical technique in creation of AVF including: (1) Success rate; (2) Time to maturation; (3) Duration of surgery; and (4) Complication rate.

METHODS

In our study we recruited 94 patients in two randomized groups and performed the AVF by the classical method or the RADAR method.

RESULTS

The RADAR group had higher primary success rate (P = 0.007), less rate of complications (P = 0.04), shorter duration of surgery (P = 0.00) and early time to maturation (0.001) when compared with the classical group. The RADAR proce-

dure is a safe and a more efficient alternative to the current classical method of AVF creation. Longer duration of follow-up is required to assess the long-term outcomes in the future.

CONCLUSION

The RADAR procedure is a safe and more efficient alternative to the current classical method of AVF creation. Longer duration of follow-up is required to assess the long-term outcomes in the future.

Key Words: Radial artery deviation and reimplantation technique; Classical technique; Arterio-venous fistula; Arterio-venous fistula trial; Dialysis fistula; Chronic kidney disease

Core Tip: Creating an arterio-venous fistula is a complex surgical procedure that often faces high failure rates. Ensuring appropriate patient selection and thorough preoperative optimization are crucial for successful outcomes. The radial artery deviation and reimplantation procedure offers a safer and more efficient alternative to the traditional method of arterio-venous fistula creation. However, extended follow-up is necessary to evaluate its long-term effectiveness.

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INTRODUCTION

Chronic kidney disease (CKD) is a burden of enormous proportion on the global health infrastructure. There are about upwards of 70 lakh patients living in CKD and with a dearth of organ donors, most of these patients remain on haemodialysis (HD). Such patients require a reliable repeatable vascular access for HD. Surgically created arterio-venous fistula (AVF) is the gold standard for HD access. Although the AVF can be created relatively quickly and under local anaesthesia, the surgery is technically demanding. Standard practice of AVF creation involves selecting the non-dominant upper limb for radio-cephalic arterio-venous fistula (RC-AVF) and selecting sites that are more proximal if it fails. The major drawback of the procedure is the poor early patency rate. Neointimal hyperplasia near the anastomotic site has been observed by a landmark paper by Sadaghianloo *et al*[1], in the mobilized segment (*e.g.*, the proximal vein mobilized to form the end-to-side anastomosis). This surgically mobilized segment coincides with turbulent flow as well as with devascularisation of the vasa vasorum; leading to intimal hyperplasia and stenosis. Therefore, a surgical technique, that minimizes venous dissection may improve rate of fistula maturation and access patency. In our study, we randomized the patients undergoing AVF creation in our institute into two groups and compared the outcomes of radial artery deviation and reimplantation (RADAR) technique *vs* the classical technique.

MATERIALS AND METHODS

The study was conducted at Department of Urology, All India Institute of Medical Sciences Jodhpur from March 2021 to September 2022. All the patients, undergoing AVF creation and considering the inclusion and exclusion criteria; were recruited in the study. The inclusion criteria were; age > 18 years, patients needing AVF for HD. The exclusion criteria were; incomplete palmar arch, previously failed AVF at wrist, severe calcification or atherosclerosis in artery, un-correctable coagulopathy, unwilling to participate, radial artery diameter < 2 mm, cephalic vein diameter of < 2 mm and/or presence of thrombosis. Sample size was calculated using the following formula for randomized control trial for statistical superiority design with dichotomous variable.

N = size per group; p = the response rate of standard treatment group (classical AVF; 60%[2,3]); p0 = the response rate of new treatment group (RADAR AVF; 85%[3]); zx = the standard normal deviate for a one- or two-sided x. Where α = 0.05, β = 0.20 and keeping in mind the fact that power of study being 80%. Minimum sample size calculated from above formula comes out to be 47 in each group. Randomization was done by computer generated random numbers. Patients' baseline assessment including the demographic characteristics, medical history, physical examination, ultrasound guidance (USG) doppler of both limbs or non-dominant limb where AVF is planned to characterises status of vessels along with routine investigations for AVF surgery. Institutional ethics and review committee, approval No. AIIM/IEC/2021/3324 was obtained to conduct the study in our institute, and informed consent for the surgery was taken during the treatment. The procedures adhered to the ethical guidelines of Declaration of Helsinki and its amendments. We confirm the availability of, and access to, all original data reported in this study. Team of urologist who were experienced in AVF

surgery performed all the procedures. All AVFs creation were performed by surgeons with substantial experience in both RADAR and conventional classic technique, ensuring proficiency in both approaches. The procedures were performed under local anesthesia. The patients undergoing the standard technique, the AVF was created with end vein anastomosed to the artery in end to side manner. The patients undergoing the RADAR technique, the radial artery was mobilized and anastomosed to the side of cephalic vein and the distal end of the cephalic vein was ligated making it a functional end to end anastomosis (Figure 1). Assessment of the following aspects were done between these two groups for comparison; time taken for completion of procedure, immediate complications in terms of bleeding, hematoma, thrombosis, gangrene, pulmonary edema, delayed postoperative complications like - steal phenomenon, venous hypertension, time to maturation of fistulas (post-operative day of starting of dialysis), primary failure rate and any re-exploration.

Statistical analysis

The data so collected was entered into an excel sheet and analysis was done using SPSS 25 (SPSS Inc, Chicago, Il, United States) software. Appropriate statistical tests were applied and *P* value of < 0.05 was regarded as significant.

RESULTS

Results and observation

Total of 107 cases were operated for RC-AVF during the study period. Of these, 94 patients were enrolled in our study and 13 patients were excluded. The excluded cases had vascular characteristics pertaining to the exclusion criteria (8 patients had vessel diameter less than that mentioned in exclusion criteria and 5 patients had incomplete palmar arch). The remaining 94 cases enrolled in our study, were divided into two groups by computer generated randomization of 47 in each. While our study includes 94 patients, which may indeed limit the generalizability of our findings, we believe it provides valuable initial insights into the comparative outcomes of RADAR *vs* conventional classic technique of AV fistula creation. The single-center nature of this study allowed us to maintain consistency in surgical protocols and data collection.

We fully agree that larger, multicenter studies are essential to validate and generalize these findings across diverse patient populations and clinical settings. This study serves as a foundation for such future research endeavors. Both the groups had similar demographic profiles and it is summarized in the following table (Table 1). When comparing the vessel diameters with maturation period, a linear correlation emerged. All the intrinsic patient specific factors which could lead to a change in outcome and can introduce a bias like, the arterial diameter, the diameter of vein, duration of CKD and duration of HD prior to surgery were evaluated for their effect on success of the surgery individually. All the patients included in the study were diagnosed with CKD stage 5 and had hypertension as the only comorbidity. Vein quality was clinically assessed and determined to have good caliber and patency, while the arterial condition in all patients was deemed to be in an apparently satisfactory state based on clinical evaluation. We acknowledge, however, that a more extensive analysis of these patient-specific variables could provide deeper insights into their potential impact on outcomes. Future studies with larger cohorts and detailed assessments of these factors will help to better delineate their influence and further refine patient selection and management strategies. The individual parameters were analyzed with *t*-test and 95% confidence interval (CI) was calculated. The intraoperative findings were also noted and compared among both the groups. The time duration taken for completion of a procedure was measured. The average duration to complete a procedure for the RADAR group was 1 hour 40 minutes, while for the classical group it was 1 hour 55 minutes. The time duration was split into 4 categories, *i.e.* < 1:30 hours, 1:31-1:45 hours, 1:46-2:00 hours, > 2:00 hours and was analyzed for statistically significance difference if any. It was noted that, in the RADAR group; the procedure could be completed relatively quickly which was statistically significant (*P* value = 0.001).

Complications

There were no cases of any death, ischemia or surgical site infection noted in either group. Two patients, one from each group had minor complications in the form of edema over the dorsum of hand and surrounding the surgical site which resolved on conservative management (limb elevation). Two patients in the RADAR group had acute onset breathlessness and pulmonary edema just after completion of the procedure. These two patients needed immediate HD for stabilization. One patient from each group underwent re-exploration for thrombosis on post-operative day 1. Comparing the complication rates in both the groups did produce a statistically significant result (*P* value = 0.044) in favor of the RADAR group.

Failure

Comparing the failure rates, 11 patients in the classical group had failure while only 2 patients in the RADAR group had failure (*P* value = 0.007). Two patients in the classical group had low flow across the AVF. Although these patients did not technically had failure, but HD could not be started during the 3 months follow-up period and they were analyzed as failure. Out of the two patients who underwent re-exploration for thrombosis in the post-operative period, one from the classical group later went on to have functional AVF, however he was evaluated as a failure in the analysis. There were no instances of abandoned AVF or secondary failures. None of the patients underwent any endovascular procedure. When comparing the all-cause complication rates for both the groups, the result came out to be statistically significant (*P* value = 0.049).

Table 1 Comparison of patient demographic profile between radial artery deviation and reimplantation and classical group, *n* (%)

Variable	RADAR (*n* = 47)	Classical (*n* = 47)	*P* value
Average age (year), mean ± SD	44.36 ± 15.85317	47.42 ± 15.85317	0.856
Sex			
Male	37 (78.7)	33 (70.2)	0.344
Female	10 (21.3)	14 (29.8)	-
Comorbidities			
HTN	44 (93.6)	42 (89.36)	0.24
DM	8 (17.02)	12 (25.53)	0.17
CAD	4 (8.51)	2 (4.25)	0.20
Others	1 (2.12)	2 (4.25)	0.28
Diameter (mm), mean ± SD			
Artery	2.18 ± 0.20358	2.18 ± 0.22824	0.159
Vein	2.29 ± 0.24181	2.36 ± 0.38086	0.200
CKD diagnosis (months), mean ± SD	2.7553 ± 2.16412	3.13 ± 2.795	0.472
HD duration (months), mean ± SD	1.64 ± 0.814	1.91 ± 1.943	0.390
BMI, mean ± SD	23.4043 ± 1.34342	22.8745 ± 1.77415	0.472

RADAR: Radial artery deviation and reimplantation; HTN: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; CKD: Chronic kidney disease; HD: Hemodialysis; BMI: Body mass index.

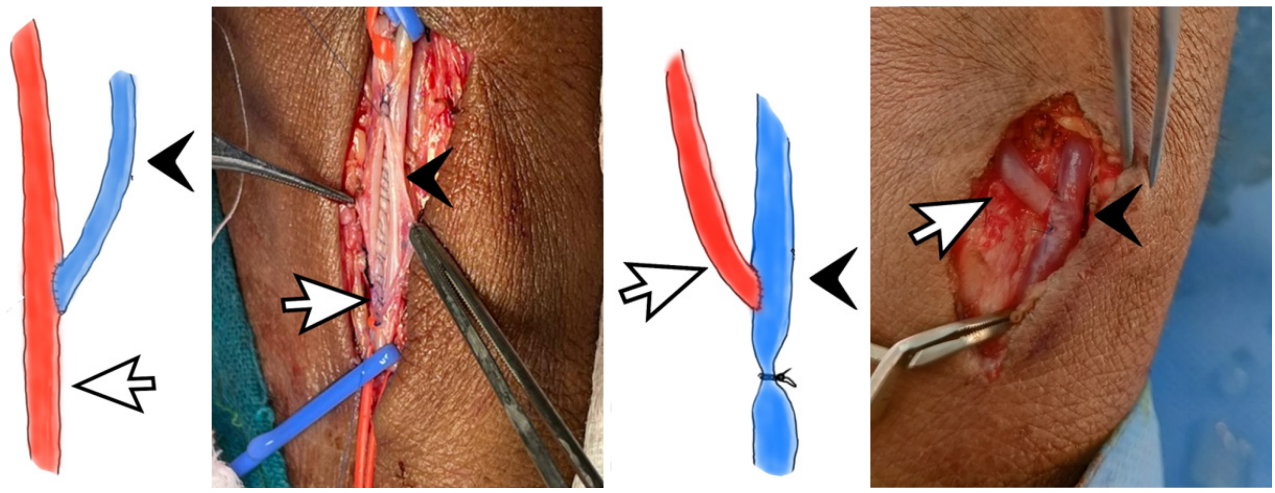

Figure 1 Radial artery deviation and reimplantation technique. White Arrow: Radial artery; Black Arrow: Cephalic vein.

While our study focuses on short- to mid-term outcomes, we acknowledge that long-term follow-up is crucial to fully evaluate the durability and patency of AVF. The current study was limited by the follow-up period of 3 months due to resource and time constraints. However, we believe it provides important preliminary data on early outcomes and complications, which are critical in the initial stages of AVF care. We agree that future studies with extended follow-up periods are necessary to assess long-term durability and patency comprehensively. This will be a priority in our subsequent research efforts.

Time to maturation

The average time to maturation of fistula was measured as when the fistula was ready to support HD. The duration of maturation period was divided into two categories for analysis, that is less than 4 weeks and more than 4 weeks. Analyzing the data, the RADAR group had statistically significant result (*P* value = 0.001).

Patency rate

Once HD was started for a patient, the patient was evaluated at the end of 3 months follow-up period to assess whether HD was being continued or not. This was the patency rates of each group. All the patients after initiation of HD had continued HD at the end of 3 months. All the patient specific factors, that can affect the surgical outcome, were analyzed to test the individual factor's influence and the results were noted (Table 2). The *P* value in the duration of maturation category came to be 0.001 which was suggestive of clinically significant outcome.

All the outcome factors, *i.e.*; success rate, complication rate, time to maturation and continuation of dialysis, were evaluated with univariate analysis to calculate the odds ratio (OR) with respect to procedure (Table 3). The RADAR group was taken as reference for calculation. The unadjusted OR for the success rate was 0.145 and the *P* value was calculated to be 0.016. The unadjusted OR for the complication rate was 2.899 and the *P* value was calculated to be 0.049. The unadjusted OR for the maturation time was 18.874 with 95%CI being 15.136 the upper and 22.613 the lower limit. The *P* value was calculated to be 0.001. The unadjusted OR for the continuation of dialysis was 0.252 with 95%CI being 0.065 the upper and 0.985 the lower limit. The *P* value was calculated to be 0.048.

The various factors which are supposed to affect the success rate were evaluated with univariate regression analysis and the unadjusted OR and 95%CI was calculated (Table 4). Out of which, the cephalic vein diameter came out to be statistically significant with *P* value being 0.003. The RADAR procedure was associated with higher success rate with *P* value being 0.016. Rest of the parameters came out to be statistically insignificant. The statistically significant factors were then analyzed for significance with multivariate analysis. The *P* value for the RADAR procedure came out to be 0.018. The *P* value for cephalic vein diameter came out to be 0.002 (Table 4).

DISCUSSION

The AVF for HD has been through many iterations over the period of years. All the forms are associated with failure rates which are quite high and the search for an ideal method is still on going. One study by Wolowczyk *et al*[4] published in January 2000 retrospectively analyzed the patency rate of RC-AVF done in the snuff box4. There were 11% occurrence of thrombosis within the first 24 hours. The maturation rate was 80% at six weeks. The patency rate was 65% at 1 year. This approach could provide with a long segment arterialization of vein with preservation of more proximal veins for further intervention if required. However, this method had higher failure rates when compared with the classical method which had failure rates around 20%-25% (Our study 23.4%). Hence this method could not gain popularity and was abandoned in favor of the classical method.

Similar results were noted by Sadaghianloo *et al*[1]. They noted that the RADAR group had excellent primary patency rates, secondary patency rates and maturation rates. There were also significantly less intervention rates. In our study, the RADAR group had similar or low complication rates when compared with the classical method and it was statistically significant (*P* value = 0.44). Two patients in the RADAR group had pulmonary edema in the immediate post-operative period needing HD. While these can be an isolated event, due to pre-existing undiagnosed cardiac condition or it might be due to the immediate high flow rates across the AVF following the RADAR procedure. In a meta-analysis conducted by Al-Jaishi *et al*[5] showed a cumulative primary failure rate of 23%. In our study, the classical group had primary failure rate of (23.4%), which is similar to previously reported studies. However, the RADAR group had significantly lower rates of primary failure rates at only 4.2%. The reason for this result may be dependent on the physics of the procedure itself.

Allon *et al*[6] evaluated the effect of preoperative mapping of vessels with USG for planning of surgery. They noted that with USG mapping and better planning, the fistulas could be made with higher success rate. The rate of adequacy increased from 46% to 54%. Marked improvement was noted among diabetic (21% to 50%) and female patients (7% to 36%). Such cases are supposedly have compromised vascular status in terms of atherosclerosis and small diameter of vessels. The initial pre-operative work-up included the USG doppler study of vessels. Our study showed that the initial diameter the veins can significantly affect the outcomes of the procedure. Irrespective of the procedure, the vein diameters were independent predictors of a successful AVF creation. A study conducted by Khavanin Zadeh *et al*[7] also found a similar relation between the preoperative vein diameter and time to maturation with a larger vein diameter resulting in a favorable outcome. This finding further solidifies the role of clinical examination before a patient is undertaken for AVF creation.

It has been known historically that, hypertension (HTN) favors AVF patency. The higher blood pressure maintains adequate flow across the newly created AVF and helps preventing thrombus formation. This observation was initially made by Feldman *et al*[8]. We had 86 (91.48%) patients with HTN which might be a leading cause of higher success rate in our study when compared with other similar studies. The duration since diagnosis of CKD to AVF creation and the period of maintenance HD have also been implicated as significant predictors of outcome. It has been observed since long that advanced uremic condition (longer duration since diagnosis of CKD to AVF creation) can lead to higher failure rates. Smith *et al*[9] in their study noted that patients undergoing AVF creation preemptively had a higher success rate. Similarly, patient who were on HD for a longer period of time had poorer outcome after AVF creation[8]. When compared for success rates of AVF creation in our study, both the CKD duration and HD duration the outcome was statistically insignificant. This is contrary to some of the previously done studies[9]. This discrepancy can be due to the fact that the time period from diagnosing CKD to performing AVF and duration of HD was relatively short.

In our study, we measured the time duration for each procedure as an indicator for ease of doing the procedure. As per our knowledge, ours is the only randomized control trial comparing the RADAR method with the classical method. Both the procedures were compared and the time duration to perform a procedure came out to be significant (*P* value = 0.001) in favor of the RADAR group. Such finding can be attributed to relative simplification of steps of doing the procedure in

Table 2 Independent *t* test between procedure and continuous variables, mean ± SD

Variable	Classical	RADAR	*P* value
Duration of CKD (months)	3.13 ± 2.795	2.76 ± 2.164	0.472
Duration of hemodialysis (months)	1.91 ± 1.943	1.65 ± .814	0.389
Radial artery diameter (mm)	2.1630 ± 2.0616	2.1872 ± 1.4237	0.509
Cephalic vein diameter (mm)	2.2277 ± 3.6576	2.3021 ± 2.3636	0.244
Time for maturation (in days)	37.78 ± 5.683	28.33 ± 5.437	0.001

CKD: Chronic kidney disease; RADAR: Radial artery deviation and reimplantation.

Table 3 Univariate regression analysis of outcomes with respect to procedure, *n* (%)

Variable	*n*	Unadjusted OR	95%CI	*P* value
Success				
RADAR (Ref)	45 (95.74)	-	-	-
Classical	36 (76.59)	0.145	0.030-0.699	0.016
Complication				
RADAR (Ref)	6 (12.8)	-	-	-
Classical	14 (29.8)	2.899	1.004-8.372	0.049
Maturation time				
RADAR (Ref)	28.33	-	-	-
Classical	37.78	18.874	15.136-22.613	0.001

RADAR: Radial artery deviation and reimplantation; Ref: Reference; OR: Odds ratio; CI: Confidence interval.

the RADAR group. Unlike other procedures, the AVF after its creation is subjected to adverse conditions continuously in the form of turbulent blood flow, pricks for HD and also the CKD status of the patient itself. Moreover, the surgical procedure itself has some inherent factors for failure. One of such factors is the angle between the two vessels being anastomosed. If the angle is too acute, then the blood flows with excessive turbulence and may lead to stenosis later. Likewise, overzealous dissection of the vein can lead to damage to the vasa vasorum of the vein. These factors lead to a cascade of abnormal wound healing and result in neointimal hyperplasia in the venous channel of the AVF. The RADAR technique addresses both these issues and this might be the cause behind the higher success rate in the RADAR group. In the RADAR technique the artery is mobilized in a gentle curve so as to make a favorable angle for anastomosis. Not disturbing the venous channel helps in preserving the vasa vasorum and possibly contributes the higher success rate in this group.

While analyzing the various patient factors in success or failure of AVF, one of the crucial factors that sometimes is overlooked, *i.e.*, the surgeon. The surgeon plays crucial role in performing any surgery and the role of the surgeon is indispensable in high stake surgeries like AVF creation. One study by Prischl *et al*[10] addresses this issue. They analyzed the outcome of AVF from various parameters including the operating surgeons. They concluded that, when the groups are matched demographically; the surgeon is the most important factor determining the outcome of the procedure. Similarly in our study, only the same group of experienced surgeons performed all the cases. The performing surgeons had more than 50 cases experience in doing the classical AVF and also performed 10 RADAR procedures each before the study was initiated. This led to standardization of surgical steps and overcame the learning curve and associated failure rates.

The timing of creating AVF is also of paramount importance. In a study published in 1998 by Hakim *et al*[11], discusses this point in detail. They noted that, early placement of a vascular access improves the survival of the access. In our study, the average duration from starting of HD to AVF creation was within 2 months, while 3 cases underwent pre-emptive AVF creation. This might be a reason behind the better outcome in our study population. This study further acknowledges the many nuances of AVF and recommends to perform vascular access surgery as early as possible for better patient outcome and AVF survival too. We found that clinical examination of veins closely corelates with outcome and also predicts a shorter duration of maturation. Malovrh *et al*[12], also found similar findings in his study. He found that proper clinical examination is as good as or even better than doppler USG in predicting the outcome. There has been only one more study comparing the classical group and RADAR group by Sadaghianloo *et al*[1]. This comparison shows that, our study is comparable to previous studies as far as the classical group is considered. The RADAR group performed

Table 4 Results of univariate regression and multivariate analysis of variables with respect to success

Univariate regression analysis			
Variable	**Unadjusted OR**	**95%CI**	***P* value**
Age (years)			
18-40 (Ref)	-	-	0.360
40-55	0.628	0.180-2.194	0.466
> 55	2.879	0.313-26.506	0.351
Sex			
Male	0.333	0.099-1.118	0.075
Female (Ref)			
CKD duration	0.909	0.742-1.114	0.358
Hemodialysis duration	1.376	0.657-2.880	0.397
BMI	1.144	0.793-1.651	0.472
Radial artery diam	3.961	0.088-178.903	0.479
Cephalic vein diam	15.969	14.160-25.856	0.003
Procedure			
Radar (Ref)	0.145	0.030-0.699	0.016
Classical			
Maturation time	0.744	0.540-1.025	0.070
Complication	0.000	0.000	0.996
Multivariate regression analysis			
RADAR (Ref)	0.091	0.013-0.663	0.018
Cephalic vein diameter	3.907	2.397-31.3	0.002

RADAR: Radial artery deviation and reimplantation; Ref: Reference; OR: Odds ratio; CI: Confidence interval; CKD: Chronic kidney disease; BMI: Body mass index.

better than many previous study cohorts.

CONCLUSION

The AVF creation is a technically demanding surgery with high failure rates. Proper patient selection and preoperative optimization is of paramount importance in success of the procedure. The RADAR procedure is a safe and more efficient alternative to the current classical method of AVF creation. Longer duration of follow-up is required to assess the long-term outcomes in the future.

FOOTNOTES

Author contributions: Sarangi SS was involved in the concept, idea, and design; Sarangi SS, Singh M, and Bhirud DP made executive contributions to the manuscript; Singh M, Bhirud DP, and Kumar S contributed to the manuscript for clinical studies, data collection; Navriya SC, Choudhary GR, and Sandhu AS contributed to implementation in patients; and all authors thoroughly reviewed and endorsed the final manuscript.

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CASE REPORT

Malakoplakia in kidney transplant recipients: Three case reports

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Abstract

BACKGROUND

Malakoplakia is a rare chronic granulomatous disease associated with gram-negative infection, predominantly by *Escherichia coli*. It is induced by defective phagolysosomal activity of the macrophages. Malakoplakia commonly affects the urinary bladder but has been shown to affect any solid organ, including the native and transplanted kidney. However, isolated malakoplakia of the kidney allograft is rare. Transplant recipients with compromised immune systems are more likely to develop malakoplakia.

CASE SUMMARY

We report three cases of kidney allograft parenchymal malakoplakia in kidney

transplant recipients on immunosuppression that were successfully managed with good outcomes. We described the clinical characteristics of all the kidney allograft malakoplakia cases documented in the literature. A total of 55 cases of malakoplakia were reported in recipients with a history of kidney transplant. A total of 27 recipients had malakoplakia involving the allograft, and others had malakoplakia in other organs. The common presentations included allograft dysfunction, pyelonephritis, and allograft or systemic mass. Most recipients had favorable outcomes with appropriate management that included prolonged antibiotic therapy and adjustment of immunosuppression. We reviewed the published literature on all the cases of malakoplakia in kidney transplant recipients so far and summarized the etiology, management, and outcomes.

CONCLUSION

This case series provides an overview of the etiology, presentation, pathogenesis, and management of malakoplakia in kidney transplant recipients.

Key Words: Renal transplant; Malakoplakia; Allograft malakoplakia; Michaelis-Gutmann bodies; Von Hansemann cells; Transplant malakoplakia; Case report

Core Tip: Patients with an immunosuppressed state, such as renal transplantation, are at increased risk of developing malakoplakia. This disease has varied presentations and is challenging to diagnose. We present our recent experience in the diagnosis and management of malakoplakia in renal transplant recipients. We were able to review the documented cases of malakoplakia among renal transplant recipients in the literature and summarize our findings. We made conclusions concerning its presentation, association with transplant rejection, and management strategies.

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INTRODUCTION

Malakoplakia is a rare chronic granulomatous disease associated with gram-negative infection, predominantly by *Escherichia coli (E. coli)*. It is induced by defective phagolysosomal activity of the macrophages. Malakoplakia commonly affects the urinary bladder but has been shown to affect any solid organ, including the native and transplanted kidney. However, isolated malakoplakia of the kidney allograft is rare.

Transplant recipients are more likely to develop malakoplakia due to compromised immune systems. We report three kidney allograft parenchymal malakoplakia cases and describe the pathological lesions of malakoplakia, particularly the pathognomonic Michaelis-Gutmann bodies, and their clinical course. We reviewed the clinical characteristics of all the post-kidney-transplant malakoplakia cases documented in the literature. We summarized recently published reports about the disease's pathogenesis, morphology, and clinical course.

CASE PRESENTATION

Chief complaints

Case 1: A 66-year-old African American (AA) male received a deceased donor kidney transplant (DDKT). The post-transplant course was complicated with *E. coli* transplant pyelonephritis, low-grade cytomegalovirus (CMV) viremia, and later recurrent urinary tract infections (UTI) within the first six months post-transplant. He was on extended-release tacrolimus (Envarsus) 20 mg daily with a target concentration of 6-8 ng/mL, Mycophenolate Sodium (Myfortic) 360 mg twice daily (due to CMV viremia), and prednisone 5 mg daily.

Six months post-transplant, he developed worsening allograft function, with creatinine concentration elevation to 2.74 mg/dL from a baseline of 1.7 mg/dL. His workup showed asymptomatic *E. coli* bacteriuria, for which he was prescribed a two-week course of oral cefpodoxime 500 mg daily.

Case 2: A 39-year-old AA female's post-transplant course was complicated by disseminated Nocardia with pulmonary and neurological lesions and ocular involvement eight months post-transplant. She completed a 12-month course of Bactrim + moxifloxacin and was noted to have residual lesions in the lungs and brain. Follow-up imaging was performed to ensure the resolution of Nocardia lesions.

Case 3: One-month post-transplant, a 62-year-old White male presented with nausea, vomiting, decreased urine output, and chills. He was on the following immunosuppressive regimen: (1) Tacrolimus 3 mg twice daily; (2) Prednisone 5 mg daily; and (3) Myfortic 500 mg twice daily.

History of present illness

Case 1: He with a past medical history of kidney cell carcinoma, a history of prostate cancer, end stage kidney disease (ESKD) due to hypertensive nephrosclerosis.

Case 2: Her with a history of ESKD secondary to type 2 diabetes mellitus (DM) and arterial hypertension (HTN) had a simultaneous pancreas and kidney transplantation.

Case 3: He with a past medical history of ESKD secondary to diabetic nephropathy and HTN had deceased donor kidney transplantation.

Physical examination upon admission

Case 1: He denied any symptoms during his follow-up in the transplant clinic. Vital signs showed a temperature of 97.3 F, blood pressure of 143 mmHg/82 mmHg, heart rate of 75/minute, and a respiratory rate of 16/minute. Physical examination demonstrated normal cardio-pulmonary findings and no allograft tenderness or peripheral edema.

Case 2: Physical examination demonstrated normal cardio-pulmonary findings. She was noted to have allograft tenderness.

Case 3: On examination, he was febrile at 101F and had dry mucus membranes and right lower quadrant abdominal transplant tenderness.

Laboratory examinations

Case 1: Urine studies demonstrated > 100 white blood cells/high power field and > 100 red blood cells/high power field. Creatinine elevation to 2.74 mg/dL from a baseline of 1.7 mg /dL. Laboratory results are detailed in Table 1.

Case 2: Laboratory evaluation showed an elevation of creatinine to 1.8 mg/dL; the other results are detailed in Table 1. Urine cultures revealed *E. coli*, and she started on IV cefepime and then switched to cefpodoxime on discharge for two weeks with plans for an outpatient allograft kidney biopsy after completion of antibiotics.

Case 3: His initial workup revealed acute kidney injury with an elevated serum creatinine concentration of 2.75 mg/dL (baseline 1.5-1.8 mg/dL); urinalysis showed pyuria and nitrites. Donor-specific antibodies were negative. Urinalysis revealed a white blood cell of 40/hpf, a red blood cell of 17/hpf, and a positive urine culture for *E. coli*. Other pertinent results at admission are shown in Table 1. He was followed up in the transplant clinic two weeks later and had an elevated serum creatine concentration of 3.01 mg/dL.

Imaging examinations

Case 1: The allograft ultrasound (US) demonstrated a 2.4 cm nodular area in the inferior pole of the kidney transplant. He subsequently underwent an initial kidney biopsy, which was positive for acute tubular injury but negative for rejection and minimal interstitial fibrosis and tubular atrophy. A magnetic resonance imaging (MRI) of the abdomen was performed for the lesion, and three complex masses within the lower pole of the right kidney transplanted pole were demonstrated.

Case 2: Computed tomography of the abdomen revealed findings consistent with acute pyelonephritis of the right lower quadrant of the kidney transplant with mild transplant hydronephrosis. A transplant kidney US showed a 3.2 cm hypoechoic mass-like area in the lower pole of the kidney transplant with hydronephrosis.

Case 3: A kidney transplant US showed a minimally complex 6.0 cm peri-transplant collection, which required placement of a drain, and the workup was consistent with a urinoma.

FINAL DIAGNOSIS

Case 1

He underwent a biopsy of the kidney mass, which demonstrated malakoplakia. Urine cultures were again positive for *E. coli*.

Case 2

She had a biopsy from the allograft kidney a month later due to worsening kidney function, which showed Banff type IA grade acute cellular rejection and malakoplakia. For case 2, histological examination showed segmental sclerosed and extensive about 70% interstitial fibrosis with proportional tubular atrophy, findings diagnostic of acute T-cell mediated rejection, grade 1A with moderate-to-severe interstitial inflammatory cells with abundant plasma cells and lymphocytes. In addition, there were focal interstitial neutrophils in addition to the plasma cells that showed rimming around tubules,

Table 1 It shows our recipients' complete blood count and chemistry results at the time of evaluation (abnormal values are highlighted in bold)

Laboratory	Case 1	Case 2	Case 3	Normal range
White blood cell	5100	11.7	5.7	4000-11000/mm^3
Hemoglobin	10.4	10.7	8.8	12-16 gr/dL
Platelet count	217000	391000	65000	150000-450000/mm^3
Na	138	135	127	136-145 mmol/L
K	5.4	4.2	4.7	3.5-5 mmol/L
Cl	106	100	96	96-106 mmol/L
HCO_3^-	24	17	21	22-26 mmol/L
Blood urea nitrogen	31.4	24.5	33	6-24 mg/dL
Creatinine	2.74	1.82	2.75	0.7-1.1 mg/dL

neutrophilic tubulitis, and focal neutrophilic casts. These findings in this recipient with a recent history of *E. coli* urinary tract infection are diagnostic of focal acute pyelonephritis. Moreover, there were focal sheets of macrophages adjacent to the area with acute pyelonephritis that have abundant PAS-positive granular eosinophilic cytoplasm (Von Hansemann cells) and basophilic inclusions that show focal targetoid appearance characteristic of Michaelis-Gutmann bodies and stained positive for calcium and iron, findings diagnostic of malakoplakia.

Case 3

The allograft biopsy was negative for rejection but showed malakoplakia.

Case 1 and Case 3

For cases 1 and 3, histological examination from the transplant biopsy showed chronic inflammatory sheets of macrophages, lymphocytes, and occasional plasma cells. Multiple intracytoplasmic inclusions with focal targetoid appearances within the macrophages were noted. These inclusions were positive for calcium on the Von Kossa stain and focally positive for Iron on the Prussian blue stain, consistent with Michaelis–Gutmann bodies pathognomonic for malakoplakia, as shown in Figure 1.

TREATMENT

Case 1

He was started on intravenous (IV) cefepime for a week and then discharged on oral Trimethoprim/Sulfamethoxazole (TMP/SMX) and the repeat imaging showed persistent biopsy-proven kidney malakoplakia three months later. He was given IV Cefepime for a week and continued on oral cefuroxime therapy for six months.

Case 2

Rejection was treated with IV thymoglobulin. Repeat urine cultures grew Acinetobacter. She was treated with IV ceftriaxone for pyelonephritis and was discharged to continue with oral TMP/SMX DS until the resolution of imaging findings.

Case 3

He was given cefuroxime for 6 months.

OUTCOME AND FOLLOW-UP

Case 1

A repeat MRI later showed decreased size in the kidney lesions, and serum creatinine concentration reached a nadir of 1.2 mg/dL.

Case 2

A follow-up MRI three months later showed complete resolution in malakoplakia and complete resolution of hydronephrosis.

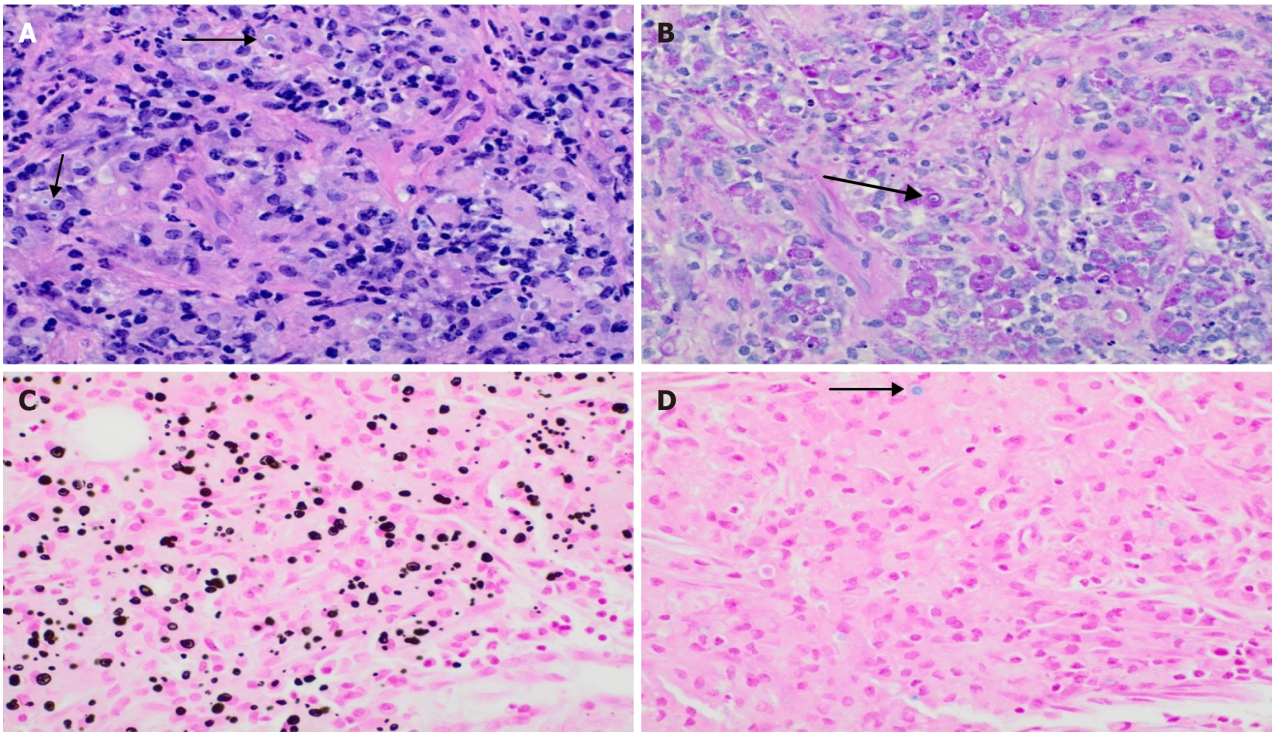

Figure 1 Von Kossa stain. A: Variable lymphoplasmacytic infiltrate and sheets of macrophages were noted on the haematoxylin and eosin stain(marked with arrows); B: Periodic acid Schiff (PAS) stain highlighting PAS positive intracytoplasmic inclusions (Michaelis-Gutmann bodies) marked with an arrow that focally has a targetoid appearance; C: Von-Kossa stain highlighting the mineralized cytoplasmic inclusions; D: Prussian blue stain for iron that is focally positive(marked with an arrow).

Case 3

A repeat kidney imaging three months later demonstrated a resolution of malakoplakia.

DISCUSSION

Malakoplakia is a rare chronic granulomatous infectious disease involving the skin and other organs[1,2]. Malakoplakia was first described by von Hansemann in 1901 and 1902 by Michaelis and Gutmann[3]. It is most frequently reported to occur in the genitourinary system. The first case of malakoplakia reported outside the genitourinary system was in 1958 [4]. Malakoplakia is believed to result from the inadequate killing of bacteria by macrophages or monocytes that exhibit defective phagolysosomal activity[5]. Reduced monocytic cyclic guanosine monophosphate (cGMP) levels and decreased release of ß-glucuronidase lead to impaired lysosomal clearance, leading to bacterial residues in macrophages. Partially digested bacteria accumulate in monocytes or macrophages and lead to the deposition of calcium and iron on residual bacterial glycolipids. The presence of the resulting basophilic inclusion structure, the Michaelis-Gutmann body, is considered pathognomonic for malakoplakia[5-7]. These macrophages with pathological Michaelis-Gutmann bodies are called Von Hansemann cells.

The most common organism isolated was *E. coli*. Other organisms isolated include Klebsiella and Proteus species. *Staphylococcus aureus* (*S. aureus*), *Pseudomonas aeruginosa*, and *Rhodococcus equi* are rarely encountered in recipients with malakoplakia[8].

An immunodeficient state favors the increased incidence of malakoplakia in immunocompromised states, including post-organ transplantation, DM, chronic alcohol intake, acquired immune deficiency syndrome, malignancy, and immunosuppressive therapy, which suggests that an impaired function of T lymphocytes may play a role in the pathogenesis of malakoplakia[3,6,7]. Partial or complete resolution of phagocytic cell dysfunction has been shown to occur in recipients with malakoplakia after cessation of immunosuppressive therapy[2,6-9].

We report these cases because of the rarity of isolated malakoplakia on kidney allografts and the scarcity of medical literature regarding management. Immunosuppression predisposes and increases kidney transplant recipients to gram-negative bacterial infections and subsequently to the development of malakoplakia. The differential diagnosis of malakoplakia includes other chronic inflammatory processes such as mycobacterium avium infections and xanthogranulomatous pyelonephritis.

In all of our cases, malakoplakia was diagnosed by biopsy, and two showed resolution of malakoplakia with TMP/SMX DS confirmed by serial imaging modalities. The other case demonstrates the complexity of managing and the need for therapy adjustments to achieve curative treatment.

Methods

We reviewed the literature in PubMed for cases of malakoplakia among kidney transplant recipients. Publications not in English were excluded, and we identified 55 cases (Figure 2) published among kidney transplant recipients (including the current 3 cases). Of the 55 reported cases, 27 involved the kidney allograft (Table 2)[7,10-30], and 28 involved other internal organs instead of the kidney allograft (Table 3)[6,9,31-54]. Out of these 28 cases of Malakoplakia involving other organs, nine involved the gastrointestinal tract, 6 involved the bladder, 5 involved the groin or perineum, 2 involved the lung, 2 involved the skin, 1 involved the prostate, 1 involved the abdominal wall, 1 involved the tongue, and 1 involved the native kidney (Table 3)[6,9,31-54].

Literature review

We noted several trends and observations based on the Malakoplakia cases involving the kidney allograft. *E. coli* was the most common organism, accounting for infections in 23 out of 27 cases (85.1%). Organisms such as *Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, psoriasis vulgaris*, and *S. aureus* were found in a few cases, along with *E. coli*. In two cases, the organism was not reported.

Malakoplakia was more likely to affect the kidney allografts in female recipients (23/27 cases), while it was more likely to occur in locations other than the kidney allograft in male recipients. The recipients' age varied between 14 and 74 in the literature.

The clinical presentation of malakoplakia varied based on its location and severity. When occurring in the kidney allograft, malakoplakia can present with unilateral kidney dysfunction, allograft pain, dysuria, lower urinary tract symptoms, or a palpable mass.

Recipients may also develop perinephric abscesses, hydronephrosis, or pyelonephritis. Laboratory results that may clue clinicians toward malakoplakia include elevated creatinine, decreased glomerular filtration rate, elevated white blood cell count, urinalysis suggestive of UTI, and a urine culture positive for bacterial organisms. As Patel *et al*[15] reported, hypercalcemia may rarely be seen. Imaging may show an enlarged allograft with a possible mass.

Biopsy serves as the best diagnostic tool for malakoplakia diagnosis. On gross examination, malakoplakia will appear as white or yellow patches, calcified plaques, or masses of the kidney autograft. Histopathologic examination reveals von Hansemann cells, enlarged macrophages with eosinophilic cytoplasm, and Michaelis-Gutmann bodies, 2-10 mm lesions within the cytoplasm of macrophages with a “bird’s eye” appearance, on light microscopy (Figure 1)[15]. The presence of periodic acid Schiff positive granules in the macrophages and CD 68 positivity can also confirm the diagnosis if the lesions stain negative for calcium in the von Kossa stain[7]. Sometimes, a repeat biopsy may be considered as these lesions may not be apparent early in the disease course[8].

The data reports a mix of recipient outcomes based on the recipient’s history of prior transplant rejection episodes among recipients with kidney allograft malakoplakia. Eight out of 27 cases reported prior transplant rejection or concomitant rejection, Eight out of 27 did not report prior rejection, and eleven out of 27 did not report this data. Regardless of a recipient’s history of transplant rejection, similar outcomes were noted in improvement *vs* kidney decline. Thus, prior or concurrent rejection may not present any clinical value in predicting recipient outcomes.

The time from kidney transplant to the onset of malakoplakia was variable among the cases, from 36 days to 12 years. No trends were found in linking infection to time after transplant, and thus, it is essential to note that infections can occur at any point, with a need for long-term surveillance.

Most recipients exhibited clinical improvement after successfully identifying kidney allograft malakoplakia, with 21 out of 27 cases (77.7%) showing improvement following treatment. Two of the cases reported no outcome, and 4/27 of the cases resulted in kidney failure. In the four cases where recipients developed kidney failure, the causes were often multifactorial, with recipients experiencing recurrent infections, advanced malakoplakia, unresponsive to medical therapy, and advanced disease presentation. Understanding these cases of malakoplakia post-kidney transplant underscores the importance of tailored management strategies to achieve favorable outcomes, as the majority of post-transplant infections exhibited positive results with appropriate treatment.

Among the relevant cases, treatment of the condition included initiating antibiotics, reduced immunosuppression therapy, and, rarely surgery. Antibiotics were selected based on susceptibility. TMP/SMX and fluoroquinolones are the preferred antibiotic choices in managing malakoplakia due to their ability to accumulate inside the macrophages. Bethanechol chloride has been shown to increase cGMP levels and can be considered an additive treatment in addition to antibiotics[7]. The antibiotic duration was based on treatment response, and the treatment response to antibiotics varied amongst the reported cases, ranging from 22 days to long-term therapy. Recipients were continued on long-term antibiotics even after response to a short-term treatment. Antibiotic therapy may be insufficient in advanced cases, and surgical intervention may be appropriate[55]. Such cases are rare and present as pseudotumor with mass effect. Antibiotics are crucial in the appropriate management of malakoplakia, and the recipients need to be maintained on prolonged antibiotic therapy even after the surgical resection of the lesions.

In some cases, it was found that reducing immunosuppression therapy may improve the response to antibiotic therapy [7]. Some immunosuppressive therapies may lead to malakoplakia due to leukotoxicity. Leukocyte toxic immunosuppressive agents such as azathioprine can increase the risk for malakoplakia. Purine synthesis inhibitors such as mycophenolate mofetil should be limited during the active treatment of malakoplakia. Episodes of rejection requiring heightened immunosuppression also increase the risk of malakoplakia. Overall, malakoplakia has a good prognosis with early identification and treatment. Proper management of immunosuppression and appropriate antibiotic therapy are crucial for resolving this condition[7,12,15].

Table 2 Depicts the clinical characteristics of recipients with kidney allograft malakoplakia

Ref.	Age (years)	Sex	Native disease	Time after transplant	Prior rejection	Organism	Antibiotic duration	Outcome
Case 1	66	M	HTN	8 months	No	*E. coli*	8 months	Improved
Case 2	39	F	HTN, DM	33 months	Yes	*E. coli*	3 months	Improved
Case 3	62	M	HTN, DM	1 month	No	*E. coli*	6 months	Improved
Vishwajeet *et al* [10], 2023	49	F	NR	12 years	Yes	*E. coli*	NR	Improved
Rustom *et al*[11], 2023	55	M	HTN	5 months	NR	*E. coli*	Long-term	Improved
Triozzi *et al*[12], 2022	40	F	Hemolytic uremic syndrome	4 months	No	*E. coli*	30 days	Improved
Yim *et el*[7], 2022	33	F	GN	6 months	Yes	*E. coli*	22 days	Improved
Park *et al*[13], 2020	59	F	DKD	6 months	NR	NR	Long-term	Improved
Lee *et al*[14], 2022	59	F	NR	18 months	Yes	*E. coli*	NR	Improved
Patel *et al*[15], 2021	45	F	GN	16 months	Yes	*E. coli*, *Klebsiella pneumoniae*	Long-term	Improved
Kalimuthu *et al* [16], 2021	41	F	NR	1 year	NR	Culture negative	NR	NR
Kinsella *et al*[17], 2021	63	F	NR	7 months	NR	*E. coli*	3 months	Improved
Kinsella *et al*[17], 2021	52	F	NR	4 months	NR	*E. coli*	6 months	Improved
Tan *et al*[18], 2021	55	F	Lithium	NR	NR	*E. coli*	4 months	NR
Khojah[19], 2020	74	F	NR	2 years	No	*E. coli*, *Enterobacter aerogenes*	Long-term	Improved
Khojah[19], 2020	62	F	NR	6 years	No	Culture-negative	6 months	Improved
Yasin *et al*[20], 2018	36	F	NR	4 years	NR	*E. coli*	14 weeks	Improved
Mookerji *et al*[21], 2018	58	M	Polycystic kidney disease	6 months	Yes	*E. coli*, *Enterobacter cloacae*	1 month	Kidney failure
Pirojsakul *et al* [22], 2015	14	F	Vesico-ureteral reflux	1 year	NR	*E. coli*	NR	NR
Keitel *et al*[23], 2014	23	F	GN	36 days	Yes	*E. coli*	28 days	Kidney failure
Honsova *et al*[24], 2012	31	F	DKD	12 years	Yes	*E. coli*, *Staphylococcus aureus*	NR	Improved
Augusto *et al*[25], 2008	56	F	Unknown	11 months	No, prior transplant	*E. coli*	10 weeks	Improved
Puerto *et al*[26], 2007	45	F	NR	2 years	NR	*E. coli*	None	Kidney failure
Pusl *et al*[27], 2006	43	F	DKD	2 years	NR	*E. coli*	2 months	Improved
McKenzie *et al* [28], 1996	29	F	GN	8 years	NR	NR	Long-term	Improved
Stern *et al*[29], 1994	55	F	GN	3 years	No	*E. coli*	Long-term	Improved
Osborn *et al*[30], 1977	46	F	Pyelonephritis	15 months	No	*E. coli*, *psoriasis vulgaris*	1 month	Improved

DKD: Diabetic kidney disease; DM: Diabetes mellitus; *E. coli*: *Escherichia coli*; F: Female; GN: Glomerulonephritis; HTN: Hypertensive kidney disease; M: Male; NR: Not reported.

Table 3 depicts the clinical characteristics of kidney transplant recipients with malakoplakia involving other organs

Ref.	Anatomical location	Age, gender	Native disease	Time after transplant	Prior rejection	Organism
Boo *et al*[31], 2023	Native kidney	40, F	End stage kidney disease	32 weeks	No	*E. coli*
Coulibaly *et al*[32], 2023	Colon	62, M	GN	NR	NR	NR
Biggar *et al*[6], 1985	Abdominal wall	32, M	Reflux	16 months	Yes	*E. coli*
Nieto-Ríos *et al*[33], 2017	Bladder	45, F	Preeclampsia	2 years	NR	*E. coli*
Graves *et al*[9], 2014	Bladder	56, F	GN	1 year	Yes	*E. coli*
Merritt *et al*[34], 1985	Bladder	64, F	NR	3 years	NR	NR
Deguchi *et al*[35], 1985	Bladder	22, F	GN	1 year	NR	*E. coli*, *Proteus mirabilis*, *K. pneumoniae*
Sian *et al*[36], 1981	Bladder	52, F	PKD	17 months	No	NR
Arnesen *et al*[37], 1977	Bladder	37, F	NR	6 months	No	*E. coli*, *Corynebacterium spp.*
Mitchell *et al*[38], 2019	Gastrointestinal	72, F	FSGS	10 months	NR	NR
Ghaith *et al*[39], 2018	Gastrointestinal	75, M	DKD, HTN	NR	Yes	NR
Koklu *et al*[40], 2018	Gastrointestinal	51, F	HTN	11 years	NR	NR
Mousa *et al*[41], 2017	Gastrointestinal	68, M	NR	NR	NR	NR
Bae *et al*[42], 2013	Gastrointestinal	55, F	GN	11 years	No	NR
Shah *et al*[43], 2010	Gastrointestinal	45, M	DKD	3 years	Yes	NR
Yousif *et al*[44], 2006	Gastrointestinal	40, M	PKD	15 months	NR	*E. coli*
Berney *et al*[45], 1999	Gastrointestinal	52, M	PKD	9 years	No	*E. coli*
Macdonald *et al* [46], 2019	Groin	48, M	Reflex	5 months	No	*E. coli*
Afonso *et al*[47], 2013	Groin	51, M	FSGS	2 years	NR	*Providentia spp.*, *Candida albicans*
Olivier *et al*[48], 2022	Groin	70, M	DKD, HTN	2 years	NR	*E. coli*, *Pseudomonas aeruginosa*
Lowitt *et al*[49], 1996	Perineum	51, M	Cervical intraepithelial neoplasia	14 months	NR	*Streptococci spp.*, *K. pneumoniae*, *Enterococcus spp.*
Leão *et al*[50], 2012	Perineum	37, M	Reflux	15 years	Yes	*Burkholderia cepacia*
Ifudu and Delaney [51], 1994	Prostate	60, M	HTN	1 year	NR	*E. coli*, *Serratia marcescens*
Lococo *et al*[52], 2016	Pulmonary	67, M	NR	1 year	NR	*Rhodococcus equi*
Biggar *et al*[6], 1985	Pulmonary	44, M	GN	31 months	NR	*E. coli*
Addison[53], 1986	Skin (eyelid)	35, M	Pyelonephritis	3.5 years	Yes	*E. coli*
Lowitt *et al*[49], 1996	Skin (temple)	67, M	DKD, HTN	1 year	NR	*E. coli*, *Streptococcus spp.*
Schwob *et al*[54], 2015	Tongue	70, M	NR	NR	NR	*E. coli*

DKD: Diabetic kidney disease; *E. coli*: *Escherichia coli*; F: Female; FSGS: Focal segmental glomerulosclerosi; GN: Glomerulonephritis; HTN: Hypertensive kidney disease; *K. pneumoniae: Klebsiella pneumoniae*; M: Male; NR: Not reported; PKD: Polycystic kidney disease.

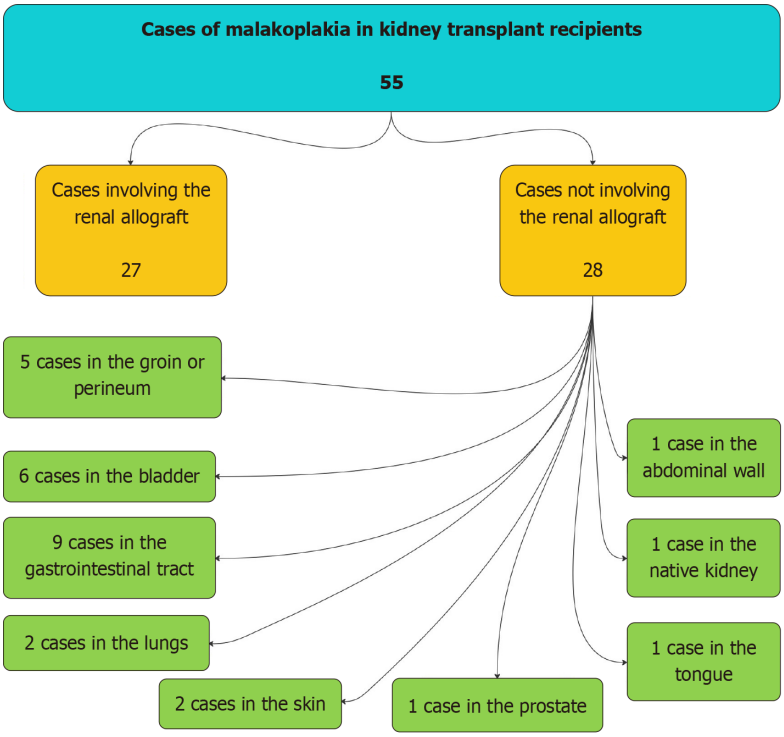

Figure 2 It shows the location of malakoplakia diagnosis in kidney transplant recipients so far documented in the literature.

CONCLUSION

Due to its rarity, atypical presentation, and progression, malakoplakia is challenging to diagnose. It should be considered in the differential diagnosis of unexplained kidney allograft dysfunction, allograft, or systemic mass in recipients with kidney transplants. Biopsy and histological examinations, such as those presented in this case series, are crucial for diagnosing Malakoplakia.

E. coli is the most common infection associated with malakoplakia in kidney transplant recipients. Malakoplakia involving the kidney allograft is common in females, whereas malakoplakia involving other internal organs is more common in males. Most recipients had favorable outcomes with appropriate management that involved administering antibiotics, adjusting immunosuppression, and, rarely resection.

Overall, this paper emphasizes the importance of having awareness and continued research in transplant nephrology as the risk for malakoplakia and its complications increases dramatically. It should be assessed in recipients with recurrent infections and unexplained loss of allograft function post-transplant. There is an increased need for guideline-based principles to address malakoplakia in kidney transplant recipients.

FOOTNOTES

Author contributions: Simhadri PK was responsible for conceptualization, wrote the original draft, literature review, and revision; Contractor R and McGee M wrote the original draft; Chandramohan D and Nangia U were responsible for literature review and revision; Atari M, Bushra S, Kapoor S, and Velagapudi RK were responsible for diagnosis, management, content validation, and revision; Vaitla PK was responsible for oversight, activity planning and execution; all of the authors read and approved the final version of the manuscript to be published.

Informed consent statement: An informed consent was obtained from all the patients described in this case series.

Conflict-of-interest statement: All authors do not have any financial or non-financial conflicts of interest concerning this submission.

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CASE REPORT

Echinococcus granulosus in atypical localizations: Five case reports

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Abstract

BACKGROUND

Hydatid cyst disease, caused by *Echinococcus granulosus*, primarily affects the liver and lungs, but it can also develop in rare locations such as the kidneys, thyroid, subcutaneous tissues, bones, and the mediastinum. These atypical presentations often pose diagnostic challenges, as they can mimic benign and malignant pathologies, leading to potential misdiagnoses and inappropriate treatments. Early and accurate detection of hydatid cysts in uncommon sites is crucial for optimal patient management.

CASE SUMMARY

This case report series presents five patients with hydatid cysts located in atypical anatomical regions: The kidney, lumbar subcutaneous tissue, gluteal soft tissue, posterior mediastinum, and thyroid gland. The patients exhibited diverse clinical symptoms, including hematuria, palpable masses, localized pain, and chronic cough. Diagnosis was confirmed through a combination of imaging techniques-ultrasound, computed tomography, and magnetic resonance imaging-along with serological testing. All cases were managed with antiparasitic therapy (albendazole), and in selected cases, surgical excision was performed to prevent complications such as cyst rupture or secondary infections. Post-treatment follow-up demonstrated complete resolution or stable cystic lesions, with no signs of recurrence.

CONCLUSION

Recognizing hydatid cysts in atypical locations is essential to avoid misdiagnosis and ensure appropriate treatment strategies. Radiological imaging plays a key role in distinguishing hydatid cysts from other cystic and neoplastic conditions, while serological tests can aid in confirmation, particularly in endemic regions. A multidisciplinary approach, integrating radiology, clinical evaluation, and surgical expertise, is critical for effective diagnosis and management. This report highlights the need for increased awareness of extrapulmonary and extravisceral hydatid disease, emphasizing its significance in differential diagnosis and clinical practice.

Key Words: Hydatid disease; Atypical localization; Renal hydatid disease; Extrapulmonary hydatid disease; Case report

Core Tip: Although the liver and lungs are responsible for 65% and 25% of Hydatid cyst illness, cysts can also occasionally develop in unusual locations like the kidneys, thyroid, bones, and subcutaneous tissue. By compressing the afflicted organs, hydatid illness can result in cysts, abscesses, and empyema. Major repercussions may ensue if it is not identified in a timely manner; if the cyst ruptures, it may cause disastrous results including anaphylaxis. A multidisciplinary approach directed by radiological data enables improved diagnosis, quicker treatment, and better patient outcomes, according to recent research and case studies.

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INTRODUCTION

Hydatid cyst disease is an endemic zoonosis caused by the parasite *Echinococcus granulosus*, which typically affects the liver and lungs[1,2]. This disease is transmitted to humans by contaminated food, where parasite eggs are disseminated through sick dogs' excrement. After entering the host's gastrointestinal tract, the parasite spreads to several organs, where it creates slow-growing, generally asymptomatic cysts. Hydatid disease can cause cysts, abscesses, and empyema by compressing the affected organs. If not detected early, it can lead to major consequences; in the event of cyst rupture, it can result in catastrophic outcomes such as anaphylaxis.

The liver accounts for 65% of the disease and the lungs for 25%; nevertheless, cysts can occasionally form in odd places such as the kidneys, thyroid, bones, and subcutaneous tissue[1]. It has an uncommon effect on the skeletal system, occurring in about 0.5-2% of instances, with the spine accounting for half of these occurrences[3]. Studies indicate that extrapulmonary hydatid cysts account for approximately 7.4% to 10.5% of intrathoracic hydatid cysts[4].

Hydatid cysts are extremely rare in subcutaneous tissues; in endemic areas, the frequency is approximately 2.3%[5]. Furthermore, some case reports claim that hydatid cysts do not form in keratinized tissues like nails and hair[6,7].

Hydatid disease has the potential to affect the entire body, as shown in Table 1[8]. This case series includes computed tomography (CT) and magnetic resonance imaging (MRI) images of three separate hydatid cysts that affect anatomical areas other than the liver and lungs.

CASE PRESENTATION

Chief complaints

Case 1: A 45-year-old woman presented with right flank pain and hematuria.

Case 2: A 43-year-old woman reported a palpable mass in the lumbar region.

Case 3: A 39-year-old woman complained of swelling and pain in the right gluteal region.

Case 4: A 77-year-old woman presented with a persistent cough.

Case 5: A 41-year-old woman was referred for evaluation of a swelling in the neck.

History of present illness

Case 1: The patient had no known comorbidities. She experienced persistent right flank pain and noticed blood in her urine.

Case 2: The patient had no prior known illnesses. She noticed a painless mass in her lumbar region, which later became tender.

Case 3: The patient had a prior history of liver hydatid cyst and lived with two dogs. She developed new symptoms of localized pain and swelling in the gluteal region.

Case 4: The patient had hypertension, diabetes, and a history of cardiac bypass surgery. She experienced a persistent cough without fever or hemoptysis.

Table 1 Location and frequency of hydatid cysts

Location	Frequency	Ref.
Liver	65%	[1]
Lung	25%	[1]
Renal	1%-3%	[6]
Brain	2%	[6]
İntrathoracic extrapulmonary	7.4%-10.5%	[4]
Muscle	2%	[6]
Skin and subcutaneous tissue	1%-2%	[6]
Heart	1%	[6]
Skeletal	0.5%-2%	[3]
Thyroid	1%	[6]
Sacral	Very rarely	[7]

Case 5: The patient had no previous illnesses but had noticed a swelling in the left side of her neck.

History of past illness

Case 1: No significant medical history.

Case 2: No significant medical history.

Case 3: Previously diagnosed with a hydatid cyst in the liver.

Case 4: History of hypertension, diabetes, and cardiac bypass surgery.

Case 5: No significant past medical history.

Personal and family history

Case 1: No relevant personal or family history.

Case 2: No relevant personal or family history.

Case 3: Frequent contact with dogs at home.

Case 4: No relevant personal or family history.

Case 5: History of dog grooming.

Physical examination

Case 1: Tenderness in the right upper quadrant of the abdomen.

Case 2: Well-defined, firm, non-mobile mass in the lumbar region.

Case 3: Localized swelling and tenderness in the right gluteal region.

Case 4: No abnormal lung sounds.

Case 5: Painless, mobile, well-defined nodule in the left thyroid lobe.

Laboratory examinations

Case 1: Urine microscopy showed mucus, epithelial cells, and erythrocytes.

Case 2: Routine blood parameters were normal; serology test positive for hydatid cyst.

Case 3: Serology test positive for hydatid cyst.

Case 4: Serology test positive for hydatid cyst.

Case 5: Thyroid function tests were normal; hydatid hemagglutination test positive.

Imaging examinations

Case 1: Renal ultrasound (US) and CT showed a multiloculated cystic lesion with septa and calcifications (Figure 1).

Case 2: Ultrasonography and MRI revealed multiloculated cystic lesions with mural and septal enhancements (Figure 2).

Case 3: CT showed hydatid cysts in the liver, lung, bone, and soft tissue (Figure 3).

Case 4: Thoracic CT revealed a cystic lesion in the posterior mediastinum (Figures 4 and 5).

Case 5: US showed a 15-mm anechoic cystic lesion in the thyroid (Figure 6).

FINAL DIAGNOSIS

Case 1: Renal hydatid cyst.

Case 2: Hydatid cyst in the subcutaneous lumbar region.

Case 3: Hydatid cysts in liver, lung, bone, and soft tissue.

Case 4: Hydatid cyst in the posterior mediastinum.

Case 5: Hydatid cyst of the thyroid gland.

TREATMENT

Case 1: Antiparasitic therapy (albendazole) and surgical intervention.

Case 2: Antiparasitic therapy (albendazole) and surgical excision.

Case 3: Antiparasitic therapy (albendazole) and surgical intervention for gluteal and bone lesions.

Case 4: Antiparasitic therapy (albendazole) and surgical excision.

Case 5: Total thyroidectomy instead of fine-needle aspiration biopsy.

OUTCOME AND FOLLOW-UP

Case 1: Follow-up imaging showed no recurrence.

Case 2: Postoperative follow-up showed complete resolution of symptoms with no recurrence.

Case 3: Follow-up imaging confirmed stability of liver and lung cysts.

Case 4: The patient recovered well with no recurrence on follow-up imaging.

Case 5: Histopathological examination confirmed the diagnosis, and no recurrence was noted during follow-up.

DISCUSSION

Hydatid cyst is a zoonotic infection caused by *Echinococcus granulosus* or, less frequently, *Echinococcus multilocularis*. It is typically transmitted to humans *via* water or food contaminated with infected dog feces. The parasite forms cysts in the human body, disrupting the function of various organs, especially the liver and lungs. When cysts form in the liver, patients frequently experience abdominal pain, a sense of fullness, and, in rare cases, jaundice. Lung cysts may cause cough, hemoptysis and shortness of breath[1]. In rare cases, other organs such as the brain, kidneys, spleen, and subcutaneous tissues may become involved, resulting in more complex clinical presentations. For example, spinal hydatid cysts can cause back and lower back pain, while cysts in the intrathoracic region can result in more complex and difficult clinical courses[4].

The prevalence of hydatid disease varies by geographical region and public health measures. Globally, the prevalence of this disease in endemic areas ranges between 1 and 200 cases per 100000 people. The Mediterranean countries, the Middle East, South America, and parts of Asia and Africa are among those hardest hits[6]. In Turkey, hydatid cyst illness is a major public health issue. According to research, the overall prevalence in Turkey ranges from 6 to 30 cases per 100000 individuals, with rates exceeding 50 cases per 100000 in some rural areas where livestock rearing is common[2]. Uncontrolled dog populations and poor hygiene standards contribute to the disease's broad prevalence in these areas[5].

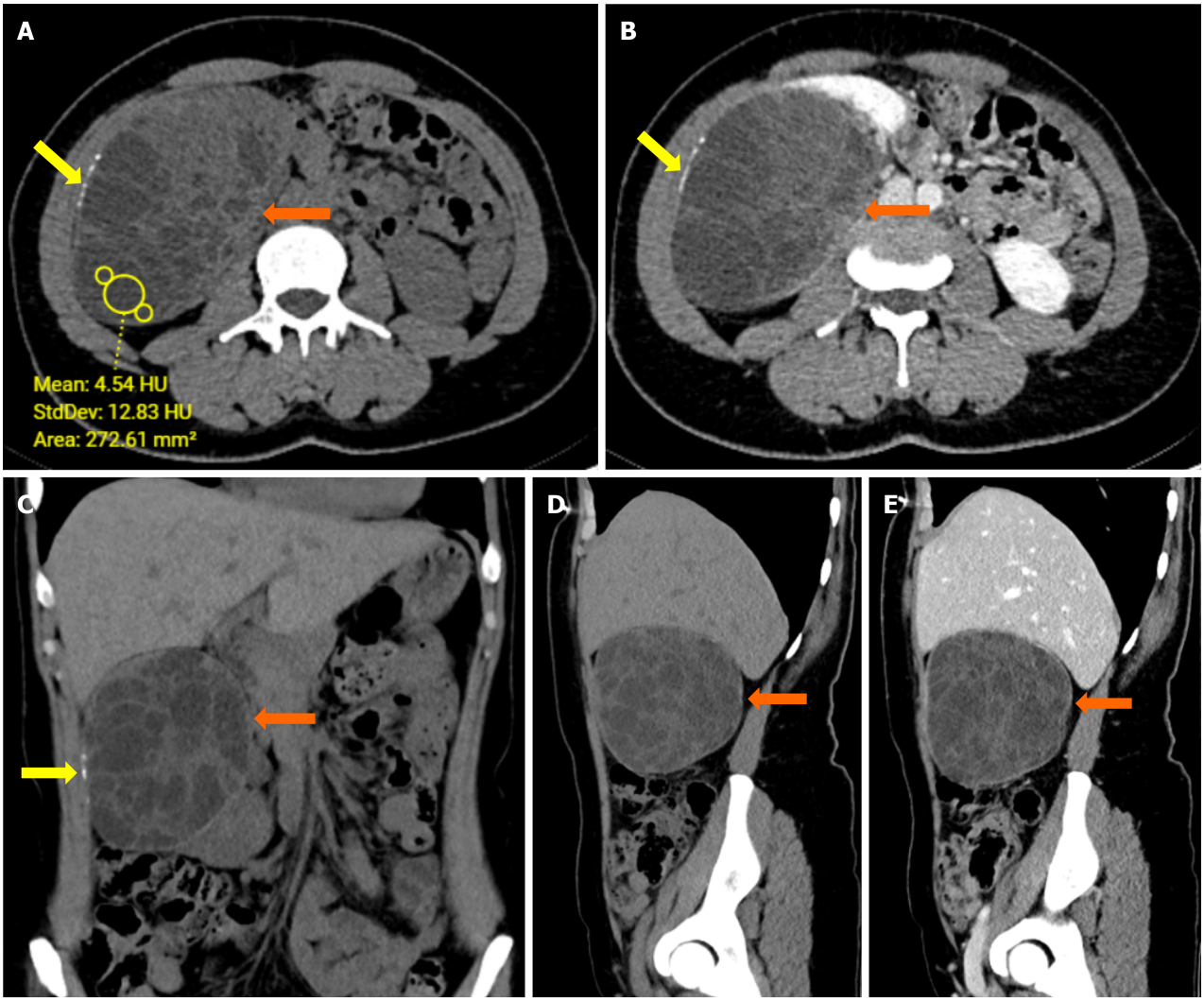

Figure 1 Axial and coronal abdominal computed tomography images of a complex cystic lesion in the right kidney. A: Axial pre-contrast computed tomography (CT) image shows a complex cystic lesion with several septations in the right kidney (orange arrows); B: Axial post-contrast CT image demonstrates enhancement of the lesion, with noticeable septations (orange arrows) and linear calcifications along its wall (yellow arrows); C: Coronal pre-contrast CT image highlights the extent of the cystic lesion and linear calcifications (yellow arrows); D: Sagittal pre-contrast CT image presents the multiloculated nature of the lesion; E: Sagittal post-contrast CT image further delineates the lesion's characteristics with contrast enhancement of the septations.

Hydatid disease is diagnosed using a comprehensive approach that includes clinical history, physical examination, serologic laboratory testing, and radiologic imaging[1]. The detection of germinal vesicles on US, CT, or MRI is critical for diagnosis[1,9].

Hydatid cysts can be categorized radiologically into four forms: Simple cyst, calcified cyst, complicated cyst, and cyst with matrix and daughter vesicles[2].

Simple cysts show up as well-defined anechoic masses on US scans, with or without septa and hydatid sand, creating tiny echogenic focus. It is thought to be diagnostic when daughter vesicles, matrix, or septa are present inside a cystic cavity. Dead, calcified cysts are indicated by posterior shadowing, whereas complex cysts may exhibit an undulating membrane as a result of the endocyst and pericyst separating[10]. Cysts containing daughter vesicles show up as irregular structures on CT imaging, while simple cysts show up as a peripherally contrasted hypodense mass lesion. Round calcified areas are the hallmark of calcified cysts, but membrane fluctuations or ruptures may be seen in complex cysts[10,11]. Additional information is provided by MRI; simple cysts show up as hyperintense on T2-weighted imaging and hypointene on T1-weighted images. After contrast administration, septa and cyst walls show enhanced thickness, and daughter cysts can be distinguished by their unique signal characteristics[10-12].

Hydatid cysts can be challenging to diagnose because their imaging features often overlap with other cystic and neoplastic conditions, including malignancies. There are many studies in the current literature on the diagnosis of hydatid cysts using radiological diagnostic tools[13,14].

In the kidneys, they may resemble multicystic RCC or cystic nephroma due to their multiloculated structure, irregular septa, and peripheral calcifications. Similarly, spinal or soft tissue hydatid cysts can be mistaken for cystic schwannomas, metastatic cystic lesions, or pyogenic abscesses. In the thyroid, they may look similar to benign colloid cysts or cystic papillary thyroid carcinoma. Differentiating hydatid cysts from these conditions is crucial, as a misdiagnosis could lead to unnecessary surgeries or inappropriate cancer treatments.

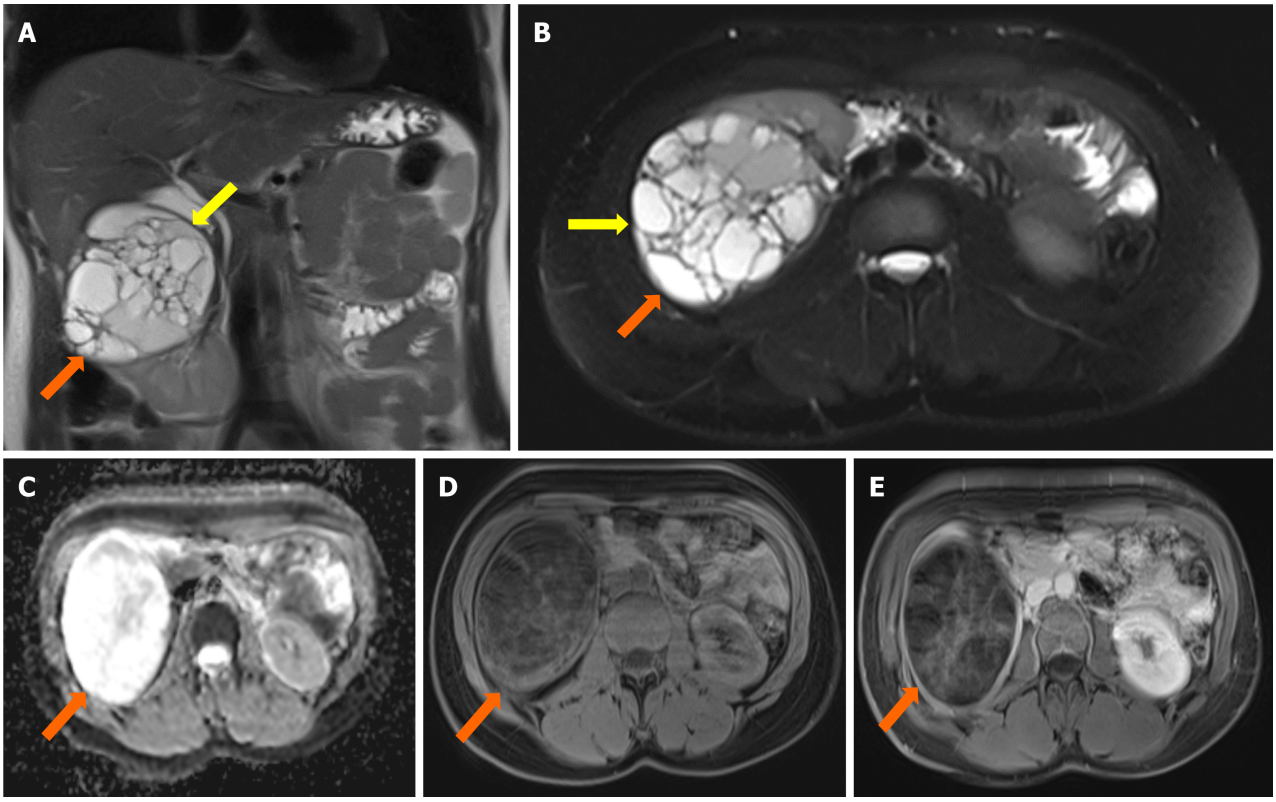

Figure 2 Coronal and axial abdominal magnetic resonance imaging of a multiloculated cystic lesion in the right kidney. A: Coronal T2-weighted (T2W) image shows a 10 cm-sized multiloculated cystic lesion in the upper part of the right kidney (orange arrows), with a hypointense rim (yellow arrows); B: Axial fat-saturated T2W image highlights the multiloculated cystic lesion (orange arrows) with a hypointense rim (yellow arrows); C: Apparent diffusion coefficient map reveals restricted diffusion within the lesion; D: Axial fat-saturated pre-contrast T1-weighted (T1W) image shows the lesion without significant enhancement; E: Axial fat-saturated post-contrast T1W image demonstrates slight contrast enhancement in the septa of the cystic lesion (orange arrows).

Imaging plays a key role in distinguishing hydatid cysts from malignant lesions. Features like floating membranes, daughter cysts, and internal septations are strong indicators of hydatid disease and are rarely seen in malignancies. On the other hand, malignant cysts typically have solid enhancing components, irregular thickened walls, and show invasive growth into surrounding tissues. Another helpful clue is rim calcification—while hydatid cysts tend to have smooth peripheral calcifications without aggressive destruction, malignant lesions often show irregular, infiltrative calcifications. Diffusion-weighted MRI and contrast-enhanced CT also help differentiate these lesions; hydatid cysts usually appear bright on T2-weighted images and show minimal enhancement, whereas malignant cysts often display heterogeneous enhancement due to their vascular nature.

Serological tests such as ELISA and Western blot for *Echinococcus granulosus* can provide additional confirmation, especially in endemic regions. However, a negative result does not always rule out the disease, as some cases may be seronegative. Therefore, an accurate diagnosis requires a multidisciplinary approach, integrating radiologic, serologic, and clinical findings to ensure proper management and avoid misdiagnosis.

Medical treatment is an important part of managing hydatid cysts and can be used in conjunction with surgery or on its own. Antiparasitic medications like albendazole and mebendazole are used to decrease cysts and reduce parasite activity. Albendazole is commonly supplied at a dose of 10-15 mg/kg per day to adults, divided into two doses in the morning and evening. The recommended treatment length is 28 days, followed by a 14-day respite, and this cycle can be repeated 2-4 times depending on the patient's condition and cyst size[9]. Mebendazole is another alternative, though less usually used, at a daily dose of 40-50 mg/kg, with therapy lasting several months. Liver function and complete blood count should be checked during treatment to avoid possible adverse effects of medical therapy, such as liver function abnormalities, gastrointestinal upset and, in rare cases, bone marrow suppression[6].

There are many studies in the literature regarding treatment protocols and follow-up of hydatid cysts[15,16]. Surgical treatment is recommended for large, symptomatic, or complicated hydatid cysts. The main surgical approaches include total cystectomy, partial cystectomy, and capitonnage. Total cystectomy involves complete cyst removal, while partial cystectomy preserves part of the cyst wall. Capitonnage is performed by closing the cavity after cyst evacuation.

The most significant risk during surgery is cyst rupture, which can lead to the dissemination of parasitic material, anaphylactic shock, and secondary cyst formation[2]. To minimize this risk, 20% hypertonic saline or povidone-iodine solution is used to sterilize the surgical field. Despite surgical removal, recurrence rates range from 10% to 30%, necessitating long-term follow-up. Postoperative albendazole therapy is recommended to eliminate any remaining microscopic parasites.

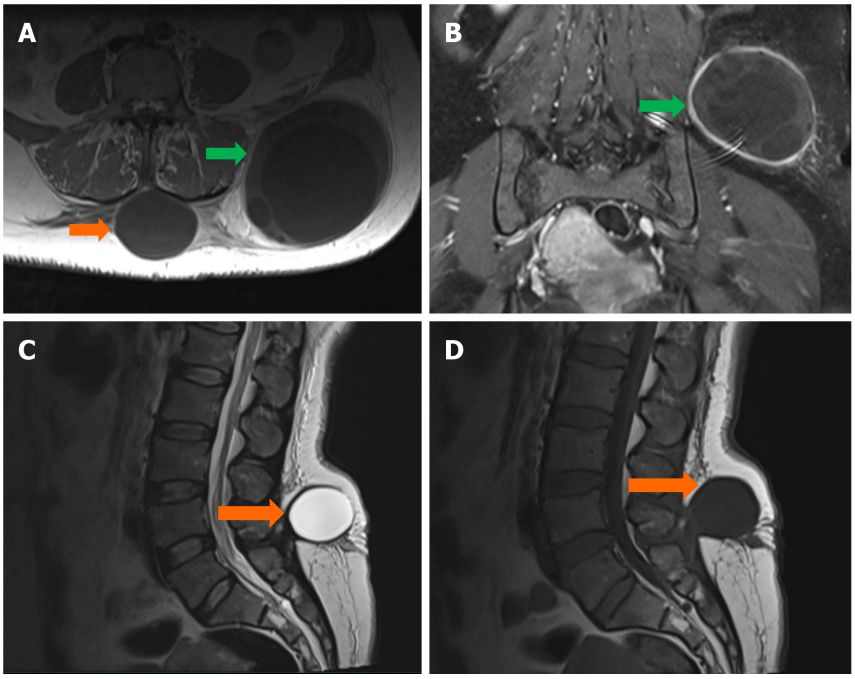

Figure 3 Lumbar region magnetic resonance imaging of multiloculated cystic lesions in the subcutaneous fat tissue. A: Axial T1W image reveals two distinct multiloculated cystic lesions in the lumbar subcutaneous fat tissue, one located in the midline (orange arrows) and the other on the left lateral side (green arrows); B: Coronal post-contrast fat-saturated T1W image shows contrast enhancement in both the septal and mural components of the lesions; C: Sagittal T2W image demonstrates the cystic nature of the lesions; D: Sagittal T1W image further characterizes the lesions with visible enhancement in their septal and mural components.

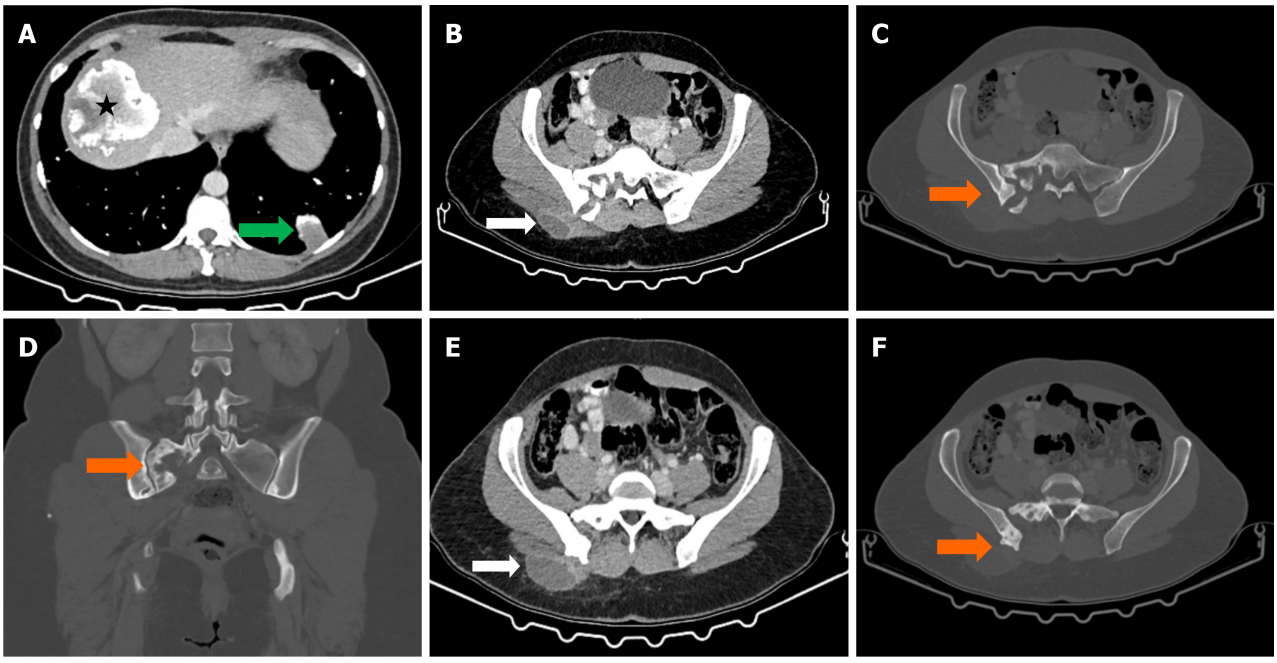

Figure 4 Abdominal computed tomography images showing inactive hydatid cysts and associated bone lesions. A: Axial abdominal computed tomography (CT) image demonstrates an inactive hydatid cyst in the right lobe of the liver (black asterisk) and another inactive hydatid cyst in the lower lobe of the left lung (green arrow); B: Axial post-contrast abdominal CT image reveals a rim-enhancing cystic lesion in the subcutaneous adipose tissue of the right gluteal region (white arrows); C: Axial bone window CT image displays erosive lesions in the right half of the sacrum (orange arrows); D: Coronal bone window CT image highlights erosive lesions in the posterior part of the right iliac wing (orange arrows); E: Axial post-contrast abdominal CT image confirms rim enhancement in the gluteal cystic lesion; F: Axial bone window CT image further depicts bone erosions in the sacrum and iliac wing (orange arrows).

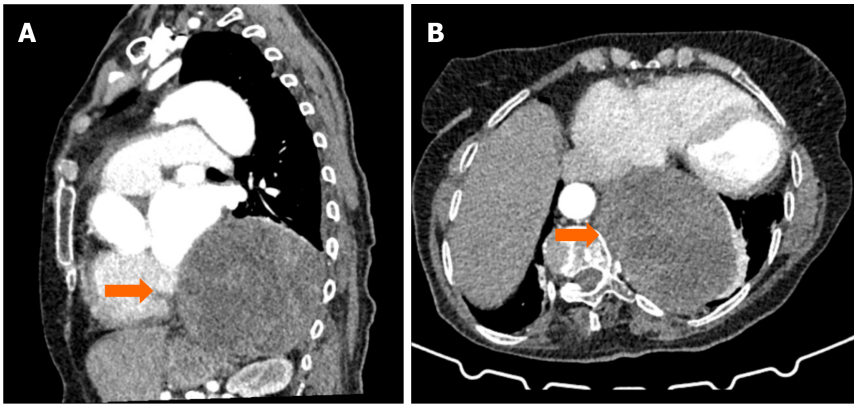

Figure 5 Thorax computed tomography images showing a cystic lesion in the left paravertebral area. A: Sagittal contrast-enhanced thorax computed tomography (CT) scan demonstrates a cystic lesion with multiple enhancing septa and smooth contours, located extrapulmonary in the left paravertebral area (orange arrows); B: Axial contrast-enhanced thorax CT image further illustrates the extrapulmonary cystic lesion with well-defined septations (orange arrows).

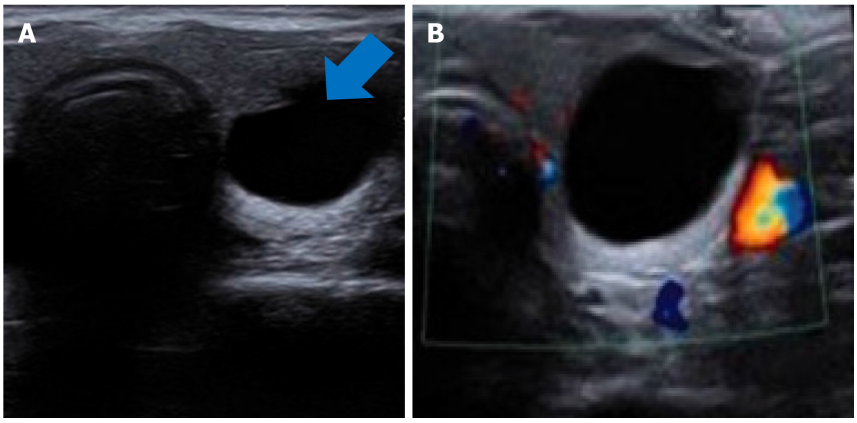

Figure 6 Ultrasound images of an anechoic cystic lesion in the left lobe of the thyroid gland. A: Anechoic cystic lesion in the left lobe of the thyroid gland (blue arrow); B: No blood flow signal was observed with ultrasound.

For patients who are not suitable candidates for surgery or are at high surgical risk, percutaneous aspiration, injection, and reaspiration (PAIR) is a minimally invasive alternative. This procedure involves aspirating the cyst content under US or CT guidance, injecting a scolicidal agent (*e.g.*, 95% ethanol or 20% hypertonic saline), and then reaspirating the fluid. PAIR is particularly effective for hepatic and renal cysts, especially those smaller than 5 cm, and has the advantage of reducing surgical complications. However, due to the risk of cyst rupture and anaphylaxis, PAIR should only be performed in experienced centers.

Hydatid disease requires long-term monitoring due to the risk of recurrence. Patients should be followed up using clinical assessment, serological tests, and imaging techniques (US, CT, MRI). Patients receiving medical treatment should be evaluated every 6 to 12 months, while post-surgical patients require follow-ups every 3 to 6 months in the first year and annually thereafter. PAIR-treated patients should undergo US evaluations at 1, 3, 6, and 12. months post-procedure. Treatment success is defined by cyst shrinkage, calcification, or complete resolution, with recurrence rates ranging from 10% to 30%.

Hydatid disease causes severe and widespread liver damage, sometimes requiring liver transplantation. This is especially important when the parasite severely inhibits liver function, causes organ failure, or has multiple cysts that cannot be treated surgically[10]. A liver transplant may also be required when the liver cannot function properly or previous surgeries have failed. Interventional treatment options might be viewed as an alternate or complementary approach to surgery. Minimally invasive treatments for hydatid cysts include percutaneous aspiration, drainage, and procedures using sclerosing agents. These operations involve aspirating fluid from the cyst with a needle under US or CT guidance, followed by injecting a sclerosing chemical to treat the cyst wall. Although percutaneous cyst resistance with albendazole treatment is a long-term treatment, especially in patients who cannot be operated on, it is sometimes the only solution to protect patients from rupture, reduce the risk of reinfection and relieve pressure symptoms. This method reduces cyst size while also neutralizing parasites. Interventional procedures are especially useful for patients who are at high surgical risk or who are not eligible for surgery, as they provide a faster recovery time[2,6].

Hydatid cysts are most typically found in the liver and lungs, although they can also form in other unusual places on the body. Atypical sites include the kidneys, spleen, brain, spine, subcutaneous tissue, and intrathoracic areas. Renal cysts can induce flank pain and urine symptoms, whereas brain cysts may cause headaches, seizures, and other neurological

symptoms[8]. Spinal hydatid cysts can cause persistent discomfort, neurological impairments, and paralysis[3,7]. Subcutaneous tissue cysts generally cause swelling and pain[5].

Atypical sites can complicate diagnosis and therapy because these cysts frequently mirror other diseases, increasing the risk of misdiagnosis. Detailed imaging and a multidisciplinary approach are required for precise diagnosis and treatment planning. The existence of cysts in unusual sites influences the selection and execution of surgical and medicinal treatment, necessitating increased attention. This article focuses on the careful evaluation of cases with unusual localizations and emphasizes the value of a multidisciplinary approach, especially in places where hydatid disease is endemic.

CONCLUSION

This study highlights that hydatid cysts can occur in atypical locations such as the kidney, thyroid, spine, and subcutaneous tissue, in addition to the liver and lungs. These rare localizations can pose diagnostic challenges and may be misinterpreted as benign or malignant conditions. The variable clinical presentation of hydatid disease necessitates a comprehensive diagnostic approach combining clinical history, serological testing, and advanced imaging. Early diagnosis is crucial for preventing complications. Treatment should be tailored based on cyst size, location, and the patient's overall condition. Medical therapy, percutaneous interventions, or surgical procedures should be selected individually, with special caution in managing atypical localizations. A multidisciplinary approach enhances diagnostic accuracy and optimizes patient management, emphasizing the clinical significance of hydatid disease. Recognizing atypical cyst locations is essential for determining appropriate treatment strategies and ensuring long term follow up.

FOOTNOTES

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CASE REPORT

Renal tubular acidosis: Varied aetiologies and clinical presentations: Three case reports

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Abstract

BACKGROUND

Renal tubular acidosis (RTA) refers to a group of kidney disorders characterized by defective acid excretion or bicarbonate reabsorption, leading to metabolic acidosis. This case series presents three cases of RTA with distinct etiologies and clinical manifestations. These cases emphasize the necessity of a comprehensive evaluation of RTA, considering both renal and systemic origins.

CASE SUMMARY

The first case describes a female patient with osteopetrosis-related RTA, diagnosed with Guibaud-Vainsel syndrome, emphasizing the importance of genetic assessment. The second case delineates RTA secondary to focal segmental glomerulosclerosis, associating tubular dysfunction with glomerular pathology. In the first two cases whole exome sequencing confirmed genetic diagnosis. The third case illuminates RTA as a complication of Graves' disease, highlighting autoimmune implications.

CONCLUSION

These cases underscore the interdisciplinary approach essential in RTA management. Understanding the diverse pathophysiology of RTA aids in tailored

therapeutic strategies and improved patient outcomes.

Key Words: Renal tubular acidosis; Guibaud-Vainsel syndrome; Marble brain disease; osteopetrosis; Focal segmental glomerulosclerosis; Graves' disease; Case series; Case report

Core Tip: Renal tubular acidosis (RTA) is characterized by systemic acidosis due to impaired ability of kidneys to excrete acid or absorb bicarbonate. The etiology is varied with both renal and extrarenal causes. Here we present three unique cases of RTA due to rare etiologies. Associated features may provide a clue to diagnosis in these cases such as osteopetrosis, thyrotoxicosis and renal failure. Whole exome sequencing may help. These cases emphasize the importance of multi-disciplinary approach to such cases for evaluation and management.

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INTRODUCTION

Renal tubular acidosis (RTA) is a heterogeneous group of disorders characterized by the impaired ability of the kidneys to excrete acid in the urine or absorb filtered bicarbonate (HCO_3^-)[1]. RTA is of four types: Type 1 (distal), type 2 (proximal), type 3 (mixed), and type 4 (hyporeninemic hypoaldosteronism)[2]. RTA may result from varying etiologies, including genetic factors, autoimmune diseases, nephrotoxins, and miscellaneous causes such as amyloidosis, sarcoidosis, obstructive uropathy, interstitial nephritis, and pyelonephritis[2]. RTA exhibits a varied spectrum of clinical manifestations, including impaired growth, failure to thrive, polyuria, polydipsia, preference for savory foods, refractory rickets, renal calculi, unexplained hypertension, and recurrent episodes of hypokalemic periodic paresis[3].

In this case series, we present three distinct cases of RTA with diverse underlying etiologies and clinical presentations: Guibaud-Vainsel syndrome with osteopetrosis, focal segmental glomerulosclerosis (FSGS), and Graves' disease. Through these cases, we aim to emphasize the need for a comprehensive evaluation in patients presenting with RTA and the importance of considering both renal and extra-renal causes. Furthermore, this case series highlights the pertinence of a multidisciplinary team in assessing and managing RTA.

CASE PRESENTATION

Chief complaints

Case 1: 30-year-old woman presented with pain and redness around her right eye, which persisted for 3 months despite treatment for conjunctivitis.

Case 2: 56-year-old man presented with progressive weakness in his upper and lower limbs over a period of 2 years. He had a right femoral neck fracture and multiple wedge compression fractures in the thoracolumbar spine. He was admitted to the orthopedics department because of these complaints.

Case 3: 54-year-old man presented with recurrent episodes of hypokalemic periodic paralysis over a period of 10 months, which was initially triggered by physical exertion.

History of present illness

Case 1: The symptoms escalated to swelling on her right cheek and mucopurulent discharge from the right side of her nose. These were accompanied by dental caries. A contrast-enhanced computed tomography (CT) scan indicated an enhancing soft tissue lesion in her right maxilla that eroded into adjacent structures. Biopsy implied osteomyelitis, and extremely hardened bones were observed intraoperatively, which was consistent with osteopetrosis.

Case 2: The patient's medical history included recurring episodes of weakness, which were treated symptomatically elsewhere. There was no history of exposure to nephrotoxic medication or any gastrointestinal disturbance. An autoimmune history was absent.

Case 3: Despite potassium correction, the patient's symptoms worsened. He experienced anxiety, weight loss, palpitations, tremulousness of hands, heat intolerance, and easy fatiguability, which preceded the paralysis attacks by 6 months.

History of past illness

Case 1: The patient had experienced global developmental delay, recurrent fractures, and hypokalemic periodic paresis since childhood. However, there was no history of hearing loss. She exhibited severe intellectual impairment and required assistance for routine daily activities.

Personal and family history

Case 1: Family history revealed second-degree consanguineous parentage. Nonetheless, similar complaints were not evident in other family members. The patient had fully developed secondary sexual characteristics, and her menstrual cycles were regular.

Physical examination

Case 1: Clinical examination showed a short stature (146 cm, below the 3rd centile), high arched palate, dental crowding, low-set ears, and malunited fractures of the bilateral shin (Figure 1).

Case 2: Physical examination revealed a fracture in the right femoral neck and multiple wedge compression fractures in the thoracolumbar spine. Despite normal vital signs and mental functions, motor weakness was noted in proximal upper and lower limbs (power 3/5), with reduced deep tendon reflexes.

Case 3: Upon admission to our clinic, physical examination suggested quadriparesis (power 2/5 in both upper and lower limbs) and acute urinary retention. However, higher mental functions, cranial nerves, and sensory examination were normal.

Laboratory examinations

Case 1: The results of laboratory examinations signified that the patient had hypokalemia with a potassium level of 2.8 mmol/L [normal range (N): 3.5-5.5 mmol/L], hyperchloremia with a serum chloride level of 115 mmol/L (N: 96-106 mmol/L), a normal anion gap of 11 mmol/L (N: 4-12 mmol/L), metabolic acidosis [pH of 7.24 (N: 7.38-7.42), serum HCO_3^- level of 15.3 mmol/L (N: 22-29 mmol/L)], and an alkaline urine pH of 7.2, consistent with RTA. Nevertheless, sodium, calcium, magnesium, urea, creatinine, and parathyroid hormone levels were within normal limits. Urinary calcium levels were normal (4.3 mmol/day, N: 2.50-7.50 mmol/day). Glucosuria or proteinuria was not noted. However, the urine could not be tested for aminoaciduria and beta 2 microglobulin owing to financial constraints.

Case 2: During admission for femoral fracture fixation, hypokalemia (potassium level of 2.6 mmol/L, N: 3.5-5.5 mmol/L), elevated serum creatinine (203.3 μmol/L, N: 52.2-91.9 μmol/L), and blood urea (6.6 mmol/L, N: 1.8-7.1 mmol/L) were observed. Blood gas analysis signified a normal anion gap [9 mmol/L (N: 4-12 mmol/L)], hyperchloremia [117 mmol/L (N: 96-106 mmol/L)], metabolic acidosis (pH: 7.27, HCO_3^-: 14 mmol/L), and an alkaline urine pH of 7.0, consistent with distal RTA. Proteinuria or glucosuria was not noted. Calcium, magnesium, and phosphorus levels were normal, and cortisol and thyroid tests were also normal. Antinuclear antibody (ANA) and anti-SSA and anti-SSB antibodies for Sjogren's syndrome were negative.

Case 3: The patient exhibited hypokalemia with a potassium level of 2.4 mmol/L (N: 3.5-5.5 mmol/L), hyperchloremia with a chloride level of 109 mmol/L (N: 96-106 mmol/L), and a normal serum sodium level of 137 mmol/L (N: 135-145 mmol/L). Arterial blood gas analysis indicated metabolic acidosis with a pH of 7.29 (N: 7.38-7.42), a serum HCO_3^- level of 17.9 (N: 22-29 mmol/L)], and a normal anion gap of 10.1 mmol/L (N: 4-12 mmol/L). The urine pH was 7.2. Proteinuria or glucosuria was not observed. Thyroid function tests showed an elevated free tri-iodothyronine level of 10.34 pmol/L (N: 4-8.3 pmol/L), an increased free thyroxine level of 50.22 pmol/L (0.25-5.0 pmol/L), and a suppressed thyroid stimulating hormone (TSH) level of < 0.05 mIU/mL (N: 0.25-5.0 mIU/mL). The TSH receptor antibody level was determined to confirm the etiology of thyrotoxicosis, which was elevated at 19.3 U/L (< 1 U/L: Negative), verifying the diagnosis of Graves' disease. Furthermore, the patient was diagnosed with diabetes and had a fasting blood glucose level of 8.5 mmol/L (N: 3.9-5.6 mmol/L), a postprandial blood glucose level of 12.9 mmol/L (n < 7.8 mmol/L), and a glycated hemoglobin level of 6.9% (N: < 6.5%). Arterial blood gas analysis indicated systemic metabolic acidosis with a pH of 7.29 (N: 7.38-7.42), serum HCO_3^- level of 17.9 (N: 22-29 mmol/L)], a normal anion gap of 10.1 mmol/L (N: 4-12 mmol/L), and an alkaline urine pH of 7.2. Proteinuria or glucosuria was not observed. Complete hemogram; liver and kidney function tests; calcium, magnesium, creatinine kinase, and total prostate-specific antigen levels; and urine analysis were normal. ANA testing using immunofluorescence was negative. The ophthalmic evaluation was unremarkable.

Imaging examinations

Case 1: Skull and limb radiographs showed features suggestive of osteopetrosis, including substantial sclerosis involving the skull and facial bones. A CT scan of the brain revealed basal ganglia calcification (Figure 2), and ultrasonography of the kidneys ruled out nephrocalcinosis.

Case 2: An ultrasound examination of the kidneys revealed bilateral medullary nephrocalcinosis.

Case 3: Thyroid ultrasound indicated that both lobes were enlarged but had normal vascularity. Technetium 99 (^{99m}Tc) thyroid scintigraphy showed uniformly increased uptake in both lobes, with uptake being 16.2% (normal 0.3%-3%), which agreed with Graves' disease.

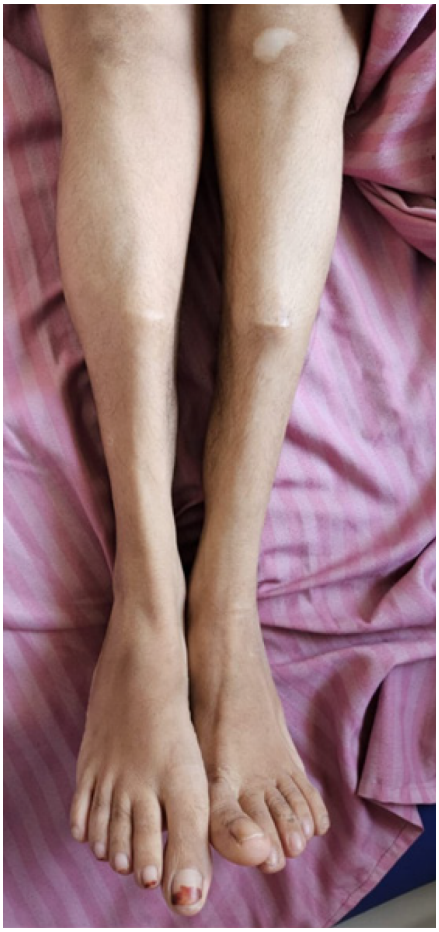

Figure 1 Malunited fractures of bilateral shin.

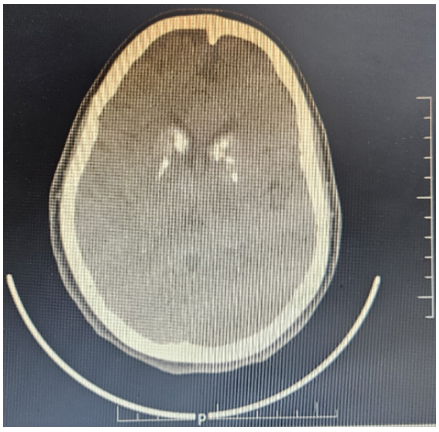

Figure 2 Computed tomography brain showing basal ganglia calcification.

FINAL DIAGNOSIS

Case 1

Guibaud-Vainsel syndrome was suspected because of the presence of the above features of RTA, severe intellectual impairment, and osteopetrosis. Homozygous deletion variant in intron 3 of the anhydrase II *(CA 2)* gene on chromosome 8 of autosomal recessive (AR) inheritance was observed on whole-exome sequencing, confirming the diagnosis of marble brain disease. A final diagnosis of Guibaud-Vainsel syndrome/Marble brain disease due to AR mutation of *CA 2* gene.

Case 2

Whole-exome sequencing identified an autosomal dominant, heterozygous missense mutation in exon 2 of the transient receptor potential channel 6 (*TRP6*) gene (chr11: g.101504735C>A; depth: 92x, typical of FSGS 2). Hence, the patient was

finally diagnosed with FSGS due to *TRP6* mutation and secondary RTA.

Case 3

The final diagnosis was periodic paresis caused by hypokalemia and normal anion gap metabolic acidosis due to distal RTA secondary to Graves' disease.

TREATMENT

Case 1

The treatment regimen involved a tablet of sodium bicarbonate 300 mg twice daily and a tablet of potassium citrate 1080 mg (equivalent to 10 mmol) twice daily.

Case 2

The patient was started on oral potassium citrate as per recommendations. Over the next 4 days, the HCO_3^- levels increased and the serum potassium levels normalized. Upper limb strength improved significantly in a week. Subsequently, fixation of the right femoral fracture was performed. A denosumab injection was administered for osteoporosis, which was evident on bone densitometry. As denosumab injection is a safe option when creatinine levels are elevated, it was considered for treating osteoporosis. Renal biopsy was not performed.

Case 3

The patient received intravenous potassium correction, resulting in the rapid resolution of quadriparesis. He was started on oral sodium bicarbonate at 3 g per day, oral potassium citrate to supplement 60 mmol/day of potassium, carbimazole 30 mg in divided doses, and propranolol 80 mg in divided doses. A venous blood gas bicarbonate level of 22 mmol/L and a serum potassium level of > 3.5 mmol/L were targeted.

OUTCOME AND FOLLOW-UP

Case 1

After a month of follow-up, metabolic acidosis and serum potassium levels improved (arterial blood pH: 7.33, serum HCO_3^- level: 20 mmol/L, and serum potassium level: 3.5 mmol/L).

Case 2

Muscular weakness improved considerably after 3 months of oral potassium citrate treatment, and the patient could walk with limited support. However, owing to financial constraints, the family could not afford Sanger sequencing.

Case 3

For Graves' disease, the patient was subjected to radioiodine ablation after 6 months of carbimazole therapy, following which he developed hypothyroidism and was switched to levothyroxine. His oral sodium bicarbonate and potassium citrate were tapered after 6 months once the thyrotoxicosis was reversed, with monthly testing of serum potassium, pH and bicarbonate levels in venous blood gas. There were no further episodes of quadriparesis during the 10 months of follow-up since diagnosis.

DISCUSSION

In this case series, we have described three distinct cases of RTA involving diverse etiologies and clinical presentations (Table 1).

Carbonic anhydrase II (*CA2*) deficiency is a rare disease classically characterized by osteopetrosis, RTA, and cerebral calcification. The first case involves a woman with a history of short stature, developmental delay, and intellectual impairment presenting with maxillofacial swelling, which on surgery, revealed features of osteopetrosis consistent with hardened bones. Osteopetrosis, or marble bone disease, is a group of rare, heritable diseases of the bone marked by an elevated bone density[4]. When combined with RTA, osteopetrosis is known as Guibaud-Vainsel syndrome or marble brain disease[5]. It follows an AR pattern of inheritance, and the clinical manifestations comprise sclerotic bones, growth failure, mental retardation, facial dysmorphism, intracerebral calcification, and conductive hearing loss. The most common cause is a *CA2* gene mutation, as observed in our patient. RTA is usually of the mixed type (type 3) in such patients[5]. Other features that can be associated with this syndrome such as optic nerve and retinal atrophy and hematological features were absent in the index case.

CA II is a zinc metalloproteinase enzyme found in various cell types, such as osteoclasts and proximal and distal tubular cells. In the proximal renal tubules, its primary role is to convert carbon dioxide (CO_2) into protons (H^+) and bicarbonate ions (HCO_3^-) to enable the absorption of HCO_3^- into the basal membrane of proximal tubular cells and subsequently into the systemic circulation[6]. The reabsorption of HCO_3^- in the proximal renal tubule requires the activity

Table 1 Summary of the cases of renal tubular acidosis

Case	Age (years)/sex	Presenting complaint	Significant medical history	Lab findings	Imaging findings	Genetic testing	Diagnosis	Therapy
1	30/F	Pain, redness around right eye, swelling on cheek, mucopurulent discharge from nose, dental caries	Consanguineous parentage, developmental delay, severe intellectual impairment, recurrent fractures, hypokalemic periodic paresis since childhood	Hypokalemia, hyperchloremic metabolic acidosis, normal anion gap, alkaline urine pH	Osteopetrosis in radiographs of the skull and limbs, basal ganglia calcification in CT scan	Homozygous deletion variant in intron 3 of *CA 2* gene	Proximal RTA (type 2)	Oral sodium bicarbonate and potassium citrate
2	56/M	Progressive weakness in limbs, femur neck fracture, thoracolumbar spine compression fractures	Proximal muscle weakness, inability to walk without support	Hypokalemia, elevated creatinine and urea, hyperchloremic metabolic acidosis, normal anion gap	Bilateral medullary nephrocalcinosis on kidney ultrasound	Heterozygous missense mutation in *TRP6* gene suggestive of FSGS 2	Distal RTA (type 1)	Oral potassium citrate, right femur fracture fixation, denosumab
3	54/M	Quadriparesis, acute urinary retention	Recurrent episodes of hypokalemic quadriparesis	Hypokalemia, hyperchloremic metabolic acidosis, alkaline urine pH, Normal anion gap, Thyrotoxicosis, Elevated TSH receptor antibody, normal ANA, Elevated FBS and HbA1C	On ultrasound diffuse enlargement of thyroid with normal vascularity. Technetium 99 (^{99m}Tc) thyroid scintigraphy showed uniformly increased uptake in both lobes, 16.2% (normal 0.3%-3%), consistent with Graves' disease	Nil	Distal RTA secondary to Graves' disease	Oral sodium bicarbonate and potassium citrate for distal RTA. For Graves' disease carbimazole, propranolol followed by radio-iodine ablation

CT: Computed tomography; CA 2: Carbonic anhydrase type 2; RTA: Renal tubular acidosis; FSGS: Focal segmental glomerulosclerosis; ANA: Antinuclear antibody; FBS: Fasting blood sugar; HbA1C: Hemoglobin A1C or glycated hemoglobin.

of membranous carbonic anhydrase type 4 (CA IV) and intracellular CA II[7]. When filtered HCO_3^- from the glomerular filtrate is reabsorbed into CO_2 by membranous CA IV, the cellular enzyme CA II converts CO_2 back into HCO_3^- and H^+, thereby completing the process of HCO_3^- absorption. A deficiency in CA II may impede HCO_3^- reabsorption, potentially contributing to acidosis.

In addition, CA II plays an indirect role in the distal acidification of urine. This enzyme is present in the intercalated cells of the distal tubule. When H^+ is secreted into the lumen by the H^+-ATPase, CA II efficiently removes the hydroxide (OH^-) produced. An intracellular acidic pH and a suitable gradient for acid secretion are thus maintained. CA II deficiency may disrupt acid secretion, resulting in systemic acidosis[8]. Hence, CA II deficiency can be linked to both proximal and distal RTA, with proximal RTA being milder than the more prominent distal RTA. In the index case, either might have been predominant which would probably become evident on follow up.

Osteoclasts in the bone play a vital role in bone resorption and remodeling to maintain bone mineral homeostasis. This activity necessitates an acidic pH generated by H^+ resulting from the conversion of CO_2 by CA II. The deficiency of this enzyme can hamper bone resorption by osteoclasts, potentially leading to osteopetrosis[9].

FSGS is a collection of podocytopathies characterized by scarring in parts of some glomeruli, with various causes that manifest as nephrotic or sub-nephrotic proteinuria. There are recognised primary, hereditary, and secondary/maladaptive types. Primary, secondary, genetic and undetermined are the categories into which a recently proposed clinicopathological categorisation separated FSGS according to aetiology[10].

Nephrotic syndrome is a common presentation of primary FSGS. The glomerular filtration barrier is disrupted in genetic forms when genes producing proteins with structural and signalling functions in the podocyte or glomerular basement membrane are mutated. The *TRP6* mutation (a mutation in the *TRPC6* gene, which encodes for a calcium channel) can lead to podocyte dysfunction, contributing to proteinuria and progressive kidney damage and is one of the genetic causes of FSGS[11]. Nonetheless, a few cases might present tubular dysfunction prior to the development of glomerular proteinuria. In this case, the tubular acidosis is secondary to the podocyte dysfunction and the glomerular damage seen in FSGS. The type of RTA seen in FSGS due to *TRP6* mutations is often type 2 (proximal). Such an association of RTA with FSGS has been reported in Dent disease, where low molecular (tubular) proteinuria rather than albuminuria was identified on urine protein electrophoresis[12].

The co-occurrence of distal RTA and FSGS has been found in Alagille and Sjogren syndrome cases[13,14]. In the index case, a variant of the TRPC6 mutation was associated with distal RTA, which has not been reported previously. The exact mechanism of RTA in these cases is yet to be elucidated. In salt-losing tubulopathies such as Bartter syndrome, chronic stimulation of the renin–angiotensin–aldosterone axis has been hypothesized to cause secondary FSGS. In contrast, distal RTA may cause secondary FSGS and glomerular proteinuria. Distal RTA is linked to medullary nephrocalcinosis either as

a cause or effect[15].

RTA secondary to FSGS associated with a *TRP6* mutation presents a complex diagnostic challenge, as it involves both glomerular and tubular dysfunction requiring a combination of clinical, histopathological and genetic testing. Presence of normal anion gap metabolic acidosis, urine pH greater than 5.5, hypokalemia, kidney stones and bone disease would suggest a diagnosis of distal RTA. If a kidney biopsy is performed, it would confirm FSGS by showing segmental sclerosis and hyalinosis in the glomeruli. There may be interstitial fibrosis and tubular atrophy, which are indicative of tubular dysfunction and chronic renal disease. Although it is not required, genetic testing for mutations might identify the underlying genetic mutation of FSGS and provide further information for prognostication.

Patients with *TRP6* mutations often have a more aggressive disease course, potentially progressing to end-stage renal disease if not managed appropriately. The combination of FSGS due to *TRP6* mutation and secondary RTA leads to a challenging clinical scenario, with a high risk of kidney decline, complications from metabolic acidosis, and a potentially poor long-term prognosis. As kidney function declines, high blood pressure may develop, further contributing to kidney damage. Chronic acidosis can cause osteomalacia, leading to bone pain and fractures. Early diagnosis and treatment are crucial for slowing the progression of the disease.

Supplementing with potassium and bicarbonate is a crucial treatment approach for distal RTA. Metabolic alkalosis may result from excessive and protracted bicarbonate administration. Prolonged alkalosis can lead to abnormalities in the calcium and potassium balance, which can impact muscle and bone health. It can also impair renal function and affect the body's potassium, sodium, and chloride levels. Arrhythmias may result from elevated potassium levels. Prolonged use of oral potassium and bicarbonate can affect nutrient absorption and digestion in general, and excessive use can cause gastrointestinal problems like bloating and nausea.

At times, distal RTA occurs secondary to autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and primary biliary cirrhosis[2]. In the first reported association between Graves' disease and RTA in 1959, hypercalciuria resulting from hyperthyroidism causing tubular damage was proposed to be the cause of the RTA[16]. Zisman *et al*[17] subsequently reported a patient with such a co-existence and examined acid excretion in another five patients of hyperthyroidism and no known renal disease. Not finding any abnormal acid excretion, they concluded that the apparent association of hyperthyroidism and RTA was merely coincidental. Jaeger *et al*[18] summarized the association of thyroid disease including hypothyroidism and hyperthyroidism with RTA in about ten cases. He observed that the RTA was not always associated with nephrocalcinosis and in some cases persisted despite resolution of the altered thyroid function, suggesting a possible immunological mechanism rather than a metabolic one. The exact mechanism of damage to distal and collecting tubules in Graves' disease is not established as no antibodies against renal tubules have been detected to date. However, TSH receptor antibodies have been suggested to cross-react with CA II, epithelial sodium channels, intercalated cells, or acid-base transporters[19]. Sparse literature has shown good long-term outcomes as reversal to euthyroid state causes improvement of hypercalciuria, thus correcting the RTA.

CONCLUSION

This case series highlights the varied etiologies and clinical presentations of RTA. This report underscores the importance of considering systemic diseases while evaluating and managing RTA. Comprehensive evaluation, including detailed medical history and laboratory investigations such as genetic studies and imaging studies, is crucial for identifying the underlying cause and providing personalized care to patients (Table 2). A collaborative multidisciplinary approach involving nephrologists, endocrinologists, geneticists, and other specialists is essential for treating patients with RTA and the associated comorbidities. Further research is needed to decipher the underlying mechanisms linking RTA to various systemic conditions and to identify optimal therapeutic strategies for improving patient outcomes.

Table 2 Approach for diagnosis and treatment of renal tubular acidosis

Step	Description
Step 1: Clinical suspicion	Evaluate for symptoms: Growth retardation, non-healing rickets/osteomalacia, bone deformities, polyuria, nocturia, salt craving, muscle weakness
Step 2: Laboratory evaluation	Determination of arterial pH and anion gap. Check for non-anion gap metabolic acidosis
	Measure serum electrolytes (hypokalemia or hyperkalemia)
	Assess urine pH (< 5.5 or > 5.5)
	Calculate urine anion gap (Na + K) –Cl
	Measure serum bicarbonate levels
Step 3: Classification of RTA	Type 1 (distal) RTA
	Non-anion gap metabolic acidosis with urine pH > 5.5

Hypokalemia, hypercalciuria, nephrocalcinosis, nephrolithiasis common

Causes of distal RTA

(1) Autoimmune causes (Sjogren's, SLE, Graves' disease, Primary biliary cholangitis, autoimmune hepatitis)

(2) Genetic [sporadic gene mutations *(SLC4A4, ATP6B1)*, Wilson's disease, hereditary fructose intolerance, primary hyperoxaluria]

(3) Drugs (amphotericin B, trimethoprim, analgesic abuse, toluene, amiloride, pentamidine)

(4) Miscellaneous (sarcoidosis, amyloidosis, obstructive uropathy, interstitial nephritis, pyelonephritis, primary hyperparathyroidism, intravascular volume depletion of any cause, CKD of any cause, focal segmental glomerulosclerosis)

Treatment: Alkali therapy [Bicarbonate supplement (2-3 mEq/kg/day)/Potassium Citrate]

Thiazide diuretics (if hypercalciuria)

Type 2 (Proximal RTA)

Non-anion gap metabolic acidosis with urine pH < 5.5

Associated with Fanconi's syndrome

Low molecular weight proteinuria

Low serum phosphate levels

Generalized aminoaciduria

Glucosuria

Causes of proximal RTA

(1) Autoimmune (Sjogren's, SLE)

(2) Genetic [Sporadic gene mutations (*SLC4A4, ATP6B1, ATP6NA1B)*, Wilson's disease, Cystinosis, Lowe's syndrome, Galactosemia]

(3) Drugs (Amphotericin B, Trimethoprim, Analgesic abuse, toluene, amiloride, pentamidine, vanadium)

(4) Miscellaneous causes (Amyloidosis, multiple myeloma, monoclonal gammopathy, light chain deposition disease, obstructive uropathy, nephrotic syndrome, medullary cystic kidney disease)

Treatment

High-dose alkali therapy (bicarbonate supplementation 5-20 mEq/kg/day)

Phosphate supplementation

Type 4 RTA (Hyporeninemic hypoaldosteronism)

Non-anion gap metabolic acidosis

Urine pH < 5.5

Hyperkalemia

Low serum aldosterone

Low direct renin concentration

Causes of type 4 RTA:

Diabetic kidney disease

CKD of any cause

Drugs (NSAIDs, ACE inhibitors, ARBs, Heparin)

Treatment

Treat the underlying cause

Dietary potassium restriction

Fludrocortisone, if aldosterone deficiency

Bicarbonate supplementation, if acidotic

Type 3 RTA (Mixed RTA)

Features of both distal and proximal RTA

Causes (Rare, autosomal recessive osteopetrosis, carbonic anhydrase deficiency)

Treatment: Similar to that of distal and proximal RTA with bicarbonate supplementation and electrolyte management

	Sometimes, features of both proximal and distal RTA may be present initially as a transient phenomenon, and on follow-up after treatment, one form may become predominant. This transient mixed presentation can occur in severe early cases of distal RTA, immature renal tubules in infants, or acquired conditions with widespread tubulopathy (autoimmune or toxic insults)
Step 4: Monitoring and follow-up	Regular monitoring of serum bicarbonate and potassium levels. Follow-up of nephrocalcinosis/nephrolithiasis, hypercalciuria, and renal functions. To adjust treatment doses based on clinical and biochemical parameters

RTA: Renal tubular acidosis; CKD: Chronic kidney disease; NSAID: Nonsteroidal anti-inflammatory drug; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

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FOOTNOTES

Author contributions: Bhandarkar A contributed to conceptualization and manuscript writing; Boro H and Varmudy A contributed to manuscript writing and editing; Bhat S contributed to conceptualization, manuscript writing and supervision; all authors have read and approved the final manuscript. Bhandarkar A and Varmudy A contributed equally to this work as co-first authors. The two authors suggested as co-corresponding authors have contributed almost equally to the manuscript and its development into its current form. Boro H has wonderful research experience and deserves to be a co-corresponding author here. A corresponding author has a prestigious position in a manuscript and an opportunity to be one is a coveted privilege. Also, having 2 designated corresponding authors has eased the process of communication with the journal.

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LETTER TO THE EDITOR

Chronic kidney disease in geriatric patients: Estimating glomerular filtration rate in older patients with comorbidities

Guido Gembillo, Luca Soraci, Domenico Santoro

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Abstract

Aging is an inevitable process that is usually measured by chronological age, with people aged 65 and over being defined as "older individuals". There is disagreement in the current scientific literature regarding the best methods to estimate glomerular filtration rate (eGFR) in older adults. Several studies suggest the use of an age-adjusted definition to improve accuracy and avoid overdiagnosis. In contrast, some researchers argue that such changes could complicate the classification of chronic kidney disease (CKD). Several formulas, including the Modification of Diet in Renal Disease, CKD-Epidemiology Collaboration, and Cockcroft-Gault equations, are used to estimate eGFR. However, each of these formulas has significant limitations when applied to older adults, primarily due to sarcopenia and malnutrition, which greatly affect both muscle mass and creatinine levels. Alternative formulas, such as the Berlin Initiative Study and the Full Age Spectrum equations, provide more accurate estimates of values for older adults by accounting for age-related physiological changes. In frail older adults, the use of cystatin C leads to better eGFR calculations to assess renal function. Accurate eGFR measurements improve the health of older patients by enabling better medication dosing. A thorough approach that includes multiple calibrated diagnostic methods and a detailed geriatric assessment is necessary for the effective management of kidney disease and other age-related conditions in older adults.

Key Words: Chronic kidney disease; Estimated glomerular filtration rate; Renal alterations;

Geriatric patients; Chronic Kidney Disease-Epidemiology Collaboration; Modification of Diet in Renal Disease; Cockcroft-Gault formula; Berlin initiative study; Full age spectrum equation

Core Tip: Older people often battle with multiple health issues, such as diabetes, high blood pressure and heart disease, making treatment considerably more challenging, particularly if they have kidney problems. This specific cohort presents a meaningful diagnostic challenge in identifying kidney problems because of the large difficulty in differentiating normal aging from early chronic kidney disease. Accurate glomerular filtration rate estimation is important to prevent misdiagnosis, improper treatment and medication errors resulting from inaccurate calculations.

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TO THE EDITOR

We read with great interest the article by Hamarat[1] "*Glomerular filtration rate and comorbidity factors in elderly hospitalizations*", recently published in the *World Journal of Nephrology*.

Aging can be defined as an inevitable phenomenon that is usually assessed by chronological age, with people aged 65 or older being defined as "older individuals"[2]. A significant proportion of older adults receiving medical care have multiple co-occurring health problems, making treatment much more difficult. Diabetes, hypertension and heart disease often co-occur and affect overall health; this combination also affects kidney function. The author of the study emphasized the link between kidney function and comorbidities in this frail population. Differentiating between normal aging and the early stages of chronic kidney disease (CKD) can sometimes be challenging, leading to delays in interventions[3]. Therefore, an accurate estimation of glomerular filtration rate (GFR) is critical, as misclassification of CKD can lead to inappropriate treatment decisions, inaccurate medication dosing, and erroneous assessments of disease severity. The Kidney Disease Improving Global Outcomes guideline classifies CKD into six categories based on GFR (G1 to G5, with G3 divided into 3a and 3b). Furthermore, it also includes staging based on three levels of albuminuria (A1, A2, and A3), with each stage of CKD further subcategorized according to the urinary albumin-creatinine ratio[4].

Experts are currently debating[5-8] the most appropriate methods for estimating GFR in older adults and adapting CKD definitions to age[9,10]. One proposed approach involves using an age-adapted definition of estimation of GFR (eGFR) and CKD stage; in this context, the use of an eGFR threshold of < 45 mL/min/1.73 m^2 to define CKD stage 3a could decrease overdiagnosis and help to create better diagnostic tools for this group[11]. Conversely, Levey *et al*[12] argued that use of an age-calibrated definition of CKD is overly complex and probably not able to solve the issue of correct CKD staging; indeed, a comprehensive assessment of CKD severity and complications is considered important for the accurate diagnosis and treatment of CKD among older people[10,13].

Impaired physical and cognitive performance, along with physical and cognitive frailty, have a negative impact on renal function and prognosis in older people. A thorough meta-analysis of data from 114 cohorts including more than 27 million people showed an increased risk of hospitalization associated with a creatinine-based eGFR of 45-59 mL/min, which was substantially higher than that observed at greater eGFR levels[14]. For this reason, choosing the appropriate equation for GFR estimation is essential, because it considerably impacts outcomes and treatment options for many older patients. In fact, several equations are used for GFR estimation, each with their own strengths and weaknesses; however, their accuracy in older patients remains debated[15,16].

In his study, Hamarat[1] used the modification of diet in renal disease (MDRD) study equation to calculate eGFR values, but relying on this single method can be controversial[1]. Comparative research indicated that the CKD-epidemiology collaboration (CKD–EPI) equation generally provides a more accurate eGFR estimate, thus prompting its use in clinical practice[17]. However, choosing the most appropriate equation requires a more detailed consideration.

The CKD-EPI 2021[18] is one of the most commonly used equations for estimating GFR worldwide, yet it can systematically overestimate renal function in older patients, leading to potential underdiagnosis of CKD[7]. Its accuracy in this population is still controversial, given evidence of a persistent U-shaped correlation between creatinine-based eGFR and mortality, indicating a possible increased risk of mortality among older patients with apparently acceptable eGFR values.

If the CKD-EPI and the MDRD equations have multiple limitations, the Cockcroft-Gault equation may underestimate the eGFR. Roberts *at al*[19] examined the differences between the MDRD equation and the Cockcroft-Gault equation in older people. While the MDRD equation appears to overestimate renal function with increasing age, the Cockcroft-Gault equation tends to underestimate it. Moreover, the results of a study on the use of the MDRD or CKD-EPI equation instead of the Cockcroft–Gault equation to assess renal function and adjust medication dosing in older patients underlined the detrimental effects of inaccurate eGFR assessment in this population. Using the MDRD and CKD-EPI equation instead of the Cockcroft–Gault equation resulted in dosing discrepancies in 20%-25% of patients and 15% of medication

prescriptions, leading to potential overdose in 95% of cases. The use of the MDRD or CKD-EPI equations led to an increased assessment of renal function, which may influence dosing decisions and drug safety in older patients[20].

As older adults often experience sarcopenia and malnutrition, creatinine-based equations alone may not be reliable, as they do not consider the age-related decline in muscle mass. In these circumstances, decreased muscle mass may lead to decreased serum creatinine, which may falsely elevate eGFR. Emerging research suggests that two alternative equations, such as the Berlin initiative study (BIS) and the full age spectrum (FAS) equation, have significantly improved the accuracy of CKD diagnosis in geriatric patients. Numerous studies have shown that the BIS/FAS equations improve eGFR estimation and predictive risk classification in older individuals[21-23]. In contrast to the CKD-EPI equation, which calculates eGFR in adults and was developed and validated in studies with an insufficient number of older patients, the BIS equation considers age-related changes in muscle mass to more accurately estimate GFR in older individuals. In contrast, the FAS equation is applicable to all age groups and is therefore beneficial for the diagnosis and management of CKD across the lifespan[22,24]. A recent meta-analysis of eGFR equations in the geriatric population found that BIS and FAS are more accurate than CKD-EPI in calculating GFR in this population[22]. The recently introduced EKFC equations represent an improvement to FAS[25] but should be tested more thoroughly in older patients.

To further improve the calculation of eGFR in older patients with decreased muscle mass, the biomarker cystatin C, which is less influenced by muscle mass variations compared to serum creatinine, has been included in the eGFR equation to improve the assessment of renal function in older adults with sarcopenia and frailty.

Confirmatory testing using eGFR based on cystatin C (eGFRcys) or on both creatinine and cystatin (eGFRcr-cys) performed around the threshold of 60 mL/min/1.73 m² may provide greater accuracy in assessing renal function[26]. Equations that incorporate cystatin C improved the specificity of CKD diagnosis and the accuracy of GFR calculations in older adults, which has implications for medication dosing and for prevention of nephrotoxic burden. Further confirmatory studies in different older populations would be desirable. Cystatin C-based eGFR (eGFRcys or eGFRcr-cys), unlike eGFRcr alone, may improve the identification of high-risk CKD patients near the diagnostic threshold[27] and help identify older adults who are more likely to benefit from early intervention against cardiovascular disease, kidney failure, and premature mortality.

In conclusion, a combined eGFR equation that includes both creatinine and cystatin C can significantly improve the accuracy of renal function assessment in older adults. This thoroughly removes the limitations associated with creatinine and cystatin-C alone and utilizes the complementary benefits of both biomarkers to improve the accuracy of GFR prediction.

FOOTNOTES

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