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Obstructive uropathy – acute and chronic medical management

Julian Yaxley, William Yaxley

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Abstract

Obstructive uropathy is an important cause of acute and chronic kidney disease. Decompression of the urinary tract is an essential aspect of treatment. The cause and aetiology of obstruction typically determine the surgical approach. Acute relief of obstruction is frequently complicated by fluid and electrolyte imbalance. Standard therapeutic interventions for acute or chronic renal failure also apply for cases of obstructive uropathy. This narrative review summarises the early and long-term medical management of obstructive uropathy.

Key Words: Obstructive uropathy; Nephrology; Urology; Post-obstructive; Diuresis

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Core Tip: Obstructive uropathy is a prevalent cause of acute and chronic kidney disease. Urinary tract decompression is the single most beneficial aspect of management; renal impairment is frequently reversible and the long-term renal prognosis is generally excellent. Subsequent medical care is an important but underappreciated supplement to surgical treatment. Acute relief of obstruction is often complicated by disorders of sodium and potassium balance and post-obstructive diuresis. Longer-term management principles are similar to those for other forms of chronic kidney disease.

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INTRODUCTION

Obstructive uropathy is an important and potentially reversible cause of acute and chronic kidney disease. It may be broadly defined as a functional or structural impediment to urinary flow with resulting renal injury. Some sources label obstructive ‘uropathy’ as the condition causing a blockage to the flow of urine and obstructive ‘nephropathy’ as the ensuing renal parenchymal disease. With an incidence of 1.7 per 1000 people[1], obstructive uropathy accounts for approximately 10% of all cases of both acute and chronic kidney disease[2,3], including 5% of the chronic dialysis population[4]. Post-renal causes of kidney disease are particularly common in paediatric and geriatric groups.

Obstructive uropathy can be classified as acute or chronic, unilateral or bilateral, partial or complete, and intrinsic or extrinsic. There is an array of causes (Table 1) affecting both the upper and lower urinary tract; obstruction may occur anywhere from the renal calyces to the urethral meatus. The single most common cause of obstructive uropathy is benign prostatic hyperplasia, probably followed by neurogenic bladder[2]. In women the most frequent aetiology is a pelvic mass, while ureteric calculi are the major contributor in middle-aged adults and patients with a solitary kidney[2,5].

Prompt urinary system decompression is vital, which may be achieved through a variety of methods depending on the cause and site of blockage. Urologists are primarily responsible for relieving obstruction and for treatment of the underlying lesion. However, collaboration with nephrologists may be requested because sudden decompression is frequently complicated by abnormal fluid and electrolyte balance and long-term renal insufficiency. Although longstanding experience and high-quality data support a spectrum of urologic interventions, limited published evidence exists to guide the medical management of obstructive kidney diseases in the acute and chronic context. Obstructive uropathy is less represented in the literature than other causes of medical kidney disease. This evidence-based narrative review outlines the acute and post-decompression medical management of obstructive uropathy.

SEARCH METHODS

A structured search of the PubMed database was undertaken from inception to September 2022, using a range of applicable search terms in various combinations, such as “obstructive uropathy”, “post-obstructive diuresis”, and “bladder decompression”. Results were screened for relevance. A broad selection of articles were obtained, including clinical trials, commentaries, and case series. Additional papers were retrieved by manually searching guidelines or article reference lists. Articles were limited to the English language. Results of this literature search were synthesised to generate this narrative review.

PATHOPHYSIOLOGY OF URINARY TRACT OBSTRUCTION AND DECOMPRESSION

Obstructive uropathy pathogenesis begins with a post-renal obstructing lesion that impedes urinary flow. A sequence of physiologic and pathophysiologic events develop thereafter, the severity of which is related to the degree of obstruction. Continuous urine production is initially maintained through normal glomerular filtration and urinary tract peristalsis, resulting in increased pressure proximal to the blockage. The high-pressure system is perpetuated by compensatory smooth muscle stretching and hypertrophy (shown macroscopically by hydroureteronephrosis). Raised upper tract pressure reduces net hydraulic pressure thereby lowering the glomerular filtration rate (GFR), and reduces renal perfusion which subsequently causes ischaemic injury. These processes beget inflammation, tubular atrophy, and interstitial fibrosis within 2 h of total obstruction[3,4]. Urinary acidification and concentration mechanisms become impaired (‘hyposthenuria’), manifesting as blood electrolyte derangements and polyuria, which are relatively unpredictable and determined by affected sections of renal cortex and medulla[6].

Unremitting obstruction will eventually lead to scarring and atony and culminate in end-stage renal failure (ESRF), over days to months. In experimental models, some renal function persists for at least 2 wk after ureteric ligation but not longer than approximately 4 wk[7,8]. The onset of complete obstruction does not induce an abrupt cessation of kidney function because once a pressure threshold is met, backward urine leakage into the interstitium occurs (‘pyelointerstitial backflow’) with subsequent lymphatic drainage[9]. This safety mechanism also explains why spontaneous rupture of the obstructed collecting system is very rare.

Relief of urinary tract obstruction results in reversal of the processes above. Convalescence may be brisk owing to functional hypertrophy of unaffected nephrons, but incomplete renal recovery is common.

Table 1 Causes of urinary tract obstruction by anatomical level

Level of urinary tract obstruction	Causes
Upper tract (kidney, ureter)	Calculi
	Tumour
	Upper tract bleeding (<i>e.g.</i> , bleeding renal cancers, traumatic)
	Anatomic abnormality (<i>e.g.</i> , pelvi-ureteric junction obstruction)
	Papillae sloughing (<i>e.g.</i> , pyelonephritis, tuberculosis)
	Ureteric stricture
	Ureterocoele
Lower tract (bladder, prostate, urethra)	Calculi
	Tumour
	Neurogenic bladder
	Benign prostatic hyperplasia
	Prostatitis
	Cystocoele
	Bleeding (<i>i.e.</i> , clot retention)
	Urethral stricture
	Posterior urethral valves
Extrinsic	Retroperitoneal fibrosis
	Aneurysm
	Pregnancy
	Faecal impaction
	Pelvic organ prolapse
	Phimosis

SURGICAL ISSUES

The site and aetiology of urinary tract obstruction determine the surgical approach. For example, an upper tract process may necessitate ureteric stenting or placement of a nephrostomy tube to achieve adequate decompression of the blocked collecting system, while lower tract pathology (which is typically prostatic in nature for men) may benefit from pharmacotherapy, bladder catheterization, or bladder outlet surgery depending on the acuity and degree of obstruction. There is a myriad of surgical options and techniques employed in the management of urinary tract obstruction, for which a full discussion is beyond the scope of this article.

Definitive urologic surgery should be delayed if possible until after the patient is medically stable and urgent decompression has been accomplished. Resuscitation and emergency drainage are particularly important in cases of obstruction-related severe renal failure or in the setting of an 'infected obstructed' kidney. Temporising interventions, such as percutaneous nephrostomy or bladder catheter insertion, almost always precede a secondary corrective procedure performed at a later date. Medical issues requiring optimisation are often encountered at this initial presentation rather than the time of elective surgery.

Rapid bladder drainage may result in decompression haematuria, or haematuria *ex vacuo*. Relief of a chronically distended bladder, which is associated with a friable bladder wall and capillary damage, leads to macroscopic bleeding in approximately 10% of cases[10]. Decompression haematuria is almost always transient and of little clinical importance. Irrigation is sometimes required. A small randomised control trial demonstrated no benefit in gradual bladder drainage compared to rapid drainage with respect to the risk of macrohaematuria[11].

It should be recognised that urgent decompression is not indicated for all patients with urinary tract obstruction. Those with chronic symptoms, for example men seen in the outpatient setting with lower urinary tract symptoms and bladder outflow obstruction, in the absence of complications are generally suitable for a trial of medical therapy which can be complemented by elective surgery where needed. Complications that should trigger immediate bladder catheterisation include hydronephrosis, chronic urinary retention (usually defined as post-void residual bladder volumes of greater than around 300

mL), and renal impairment (obstructive uropathy).

FLUID MANAGEMENT

Clinical background and genesis

Sudden reversal of obstruction is followed by a polyuric phase in approximately two-thirds of patients with obstructive uropathy[12]. Polyuria is typically a physiologic response in which the kidney aims to restore euvolaemia and normal plasma concentrations, conceptually similar to the polyuric phase of recovering acute tubular necrosis. This osmotic diuresis of retained fluid, urea, and other nitrogenous solutes usually resolves within 24 h.

Prolonged or marked polyuria may be pathologic and extend beyond the reestablishment of homeostasis. The working term for this clinical situation is post-obstructive diuresis (POD). POD is defined as urine output greater than 200 mL/h for at least 2 consecutive hours or a urine output exceeding 3 L in 24 h[12,13]. POD seldom lasts longer than 48 h. Mechanisms of POD include impaired urinary concentrating ability due to aquaporin downregulation and loss of medullary tonicity, and dysfunction of tubular transporters because of cell apoptosis. POD affects approximately 2% of patients with complete unilateral obstruction and up to 50% of patients with bilateral obstruction[14,15]. Risk factors include complete or chronic obstruction. Risk is also proportionate to the creatinine elevation and residual bladder volume at the time of presentation; a bladder volume greater than 1500 mL prior to decompression is often associated with POD[13,16].

Treatment

Mild polyuria typically resolves without any intervention within a few hours or days and oral hydration as an outpatient therapy is generally sufficient. Patients are generally asymptomatic apart from occasional postural hypotension. Patients should be instructed to drink to thirst and avoid dehydration with a minimal daily fluid intake of approximately 2 L or 25 mL/kg. Self-monitoring of urine colour can be a simple guide allowing patients to assess their hydration status.

POD, a significant diuresis beyond 2 d, or any episodes of hypotension warrant hospitalisation for observation and fluid replacement because of the risk of electrolyte abnormalities or hypovolaemia, which may precipitate cardiovascular collapse. Regular monitoring of vital signs, an accurate fluid balance chart, and daily weights are essential. Postural blood pressure checks are also useful. Hourly urine output measurement is indicated until patient condition settles. The urine drainage catheter should be allowed to drain freely without intermittent clamping as this allows accurate assessment of urine output; historical concerns surrounding rapid decompression are unfounded, as free drainage has not been reliably shown to be associated with more complications than gradual decompression[17,18].

There is no consensus on the best fluid replacement strategy in POD and treatment must be individualised. Controlled trials to inform practice are absent. Fluid prescribing can be complex in post-obstruction patients with ongoing losses, haemodynamic instability, and electrolyte abnormalities. POD is a unique scenario where replacement fluid is administered to patients who are volume-overloaded, in anticipation of steady ongoing losses. A useful strategy is to mentally separate the patient with POD into a volume-overloaded phase and a volume-depleted phase. In the initial volume-overload phase, a preferred method is to administer intravenous fluids at 50% the rate of the preceding hour's urine output. This allows for controlled weight loss and downward titration of intravenous fluid replacement without driving endless diuresis. Crystalloid solutions are recommended rather than colloid; the type of crystalloid depends on the subject's biochemical parameters. Enteral solutions may be appropriate in reliable patients who can manage comfortably. Should an ensuing hypovolaemic phase occur, standard resuscitation principles apply; therapy should account for deficits, maintenance requirements, and ongoing losses. Most patients do not reach a hypovolaemic phase as they successfully achieve homeostasis and diuresis abates with decremented fluid replacement.

ELECTROLYTE DERANGEMENTS

Clinical background and genesis

Obstructive uropathy may be complicated by a number of electrolyte abnormalities, both before and after acute relief of obstruction, particularly in the context of high-grade chronic obstruction[19]. Laboratory findings vary depending on the degree of corticomedullary damage, GFR, and volume status. Early post-renal obstruction generally produces a state of tubular solute wasting, notably of sodium, potassium, bicarbonate, magnesium, calcium, and phosphate. As renal function declines, these abnormalities may be accompanied by gradual retention of potassium, hydrogen, chloride, and ammonium. Obstructive uropathy is a relatively common cause of proximal and distal renal tubular acidosis. Findings may be indistinguishable from other causes of acute or chronic kidney injury.

Sodium and potassium disorders are the most serious and frequent considerations in practice. Although the majority of cases are mild, life-threatening or refractory presentations are sometimes encountered. An overview of the management of sodium and potassium disorders in the setting of urinary tract obstruction is presented below. Other acid-base and electrolyte problems are clinically insignificant without ESRF and will not be discussed in this review.

Hyponatraemia

Hyponatraemia as a consequence of plasma dilution and tubulopathy is a common finding. It often takes several weeks following decompression before plasma sodium concentration returns to a normal range[20]. Mild hyponatraemia between 130-135 mmol/L requires no specific treatment because it should not be associated with symptoms or clinical complications. Liberal fluid intake should be avoided and a normal diet encouraged, effectively being a fluid restriction in the face of post-decompression polyuria. However, for obvious hypervolaemic hyponatraemia, standard fluid restriction is appropriate.

Moderate or severe hyponatraemia requires strict monitoring of fluid balance and plasma sodium. The frequency of blood testing must be decided on a case-by-case basis. Severe hyponatraemia is defined as a plasma sodium level below 120 mmol/L or the presence of hyponatraemia with neurological dysfunction. Like all electrolyte disturbances, the basic treatment strategy for severe hyponatraemia must establish the body's electrolyte deficit, the desired rate of correction, and the ongoing losses. There are many methods to estimate sodium balance and suitable replacement regimens, one of which is shown in [Supplementary Table 1](#). While useful, prediction formulas are relatively inaccurate and should be interpreted within the overall clinical picture. Sodium replenishment should be adjusted according to patient progress and serial blood sampling; gradual correction is preferable. With respect to POD, although precise sodium calculations can be attempted, administration of intravenous 0.9% sodium chloride at half the urine output rate is ultimately sufficient in the majority of cases.

Transurethral resection of the prostate (TURP) is a widespread surgical treatment for patients with obstructive uropathy, and the TURP syndrome therefore warrants special mention. TURP syndrome is characterised by dilutional hyponatraemia developing early post-TURP due to absorption of hypotonic irrigation solution through open prostatic venous sinusoids. Patients can absorb more than 1 L of fluid intraoperatively in this way. This potentially life-threatening syndrome is becoming increasingly rare as recognition and preventative measures improve. Use of bipolar diathermy with isotonic irrigation solution has reduced its incidence. TURP syndrome is usually effectively managed with fluid restriction and diuretics.

Hypernatraemia

Prolonged diuresis of dilute urine may result in a hypernatraemic volume-depleted state. Such patients require net rehydration rather than tapered chasing of the urine output. The incidence of hypernatraemia in obstructive uropathy is unknown but appears relatively small. Onset is typically several days post-decompression. All episodes are serious due to the risk of cerebral oedema; hypernatraemia is probably among the strongest predictors of death in individuals with POD.

Like the management of hyponatraemia, treatment is based on an estimate of water deficit and ongoing losses and is regularly adjusted according to response. Hypotonic crystalloid such as 5% glucose should be used to reach a target plasma sodium at the upper limit of normal at 145 mmol/L ([Supplementary Table 2](#)).

Hypokalaemia

Hypokalaemia is the commonest electrolyte abnormality of obstructive uropathy. It is most often encountered immediately after relief of obstruction due to urinary wasting and is self-limiting; approximately 30% of episodes of POD are associated with hypokalaemia[21]. Potassium supplementation can be difficult to predict and usually requires repeated assessment and titration. As a general rule, each 1 mmol/L fall in plasma potassium concentration equates to a body deficiency of around 200 mmol. Oral potassium replacement is generally adequate and is guided by biochemistry results, ensuring a serum level greater than at least 2.5 mmol/L but ideally above 3.5 mmol/L. Insoluble and effervescent potassium tablets each contain approximately 8 mmol and 14 mmol of potassium, respectively. Severe hypokalaemia with plasma potassium below 2.5 mmol/L deserves cardiac monitoring and intravenous replacement. The maximum daily dose by any route must be less than 400 mmol to avoid malignant arrhythmias. Simultaneous magnesium supplementation is necessary for concurrent hypomagnesaemia.

Hyperkalaemia

Post-renal obstruction complicated by severe renal impairment or focal injury of the distal tubules may give rise to hyperkalaemia. Hyperkalaemia is mostly a sign of established renal failure from a chronic process but can also occasionally evolve after prolonged post-decompression diuresis in subjects with normal kidney function.

Potassium-lowering therapies are not usually necessary since potassium homeostasis rapidly resets following collecting system decompression. Although hyperkalaemia treatment has not been widely studied in the specific context of uropathies, it is a well-known medical emergency and typical pharmacologic regimens apply. Readers should refer to standard reference texts. Retrospective data demonstrates that haemodialysis is utilised in fewer than 15% of acute hospitalisations for obstructive uropathy[22]. Patients requiring dialysis from the time of index presentation almost always imply undetected chronic urinary tract obstruction.

PERIOPERATIVE MEDICATION MANGEMENT

Medication adjustments are frequently necessary following urinary tract decompression. For example, dosing is influenced by kidney function which is frequently poor and fluctuating in this scenario, and nephrotoxins should be withheld. Common considerations are listed in Table 2.

PHARMACOLOGIC THERAPY FOR OBSTRUCTIVE UROPATHY

It is usually appropriate for patients with obstructive uropathy to receive nephrology follow-up. There is no directly proven reno-protective medical therapy for obstructive uropathy beyond standard measures such as cardiovascular risk factor reduction and proteinuria-lowering agents. Statins have improved renal recovery in animal studies but there is no supporting data in humans[23].

Angiotensin-converting enzyme (ACE) inhibitors appear similarly as effective for long-term renal preservation as in other causes of chronic kidney disease (CKD), but may aggravate injury if introduced too early post-obstruction[3,24-26]. Hypertension is prevalent among individuals with obstructive uropathy and, like in all forms of CKD, is associated with worse outcomes. Guideline-directed antihypertensive therapy is recommended[27].

Sodium-glucose transport protein 2 (SGLT2) inhibitors demonstrated an anti-fibrotic effect when introduced in laboratory rats exposed to iatrogenic ureteric obstruction[28]. In the Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) randomised control trial, the group randomised to SGLT2 inhibitor treatment, including a small number of subjects with obstructive uropathy, experienced significant renal and cardiovascular benefits[29]. SGLT2 inhibitor use in the presence of an indwelling catheter or instrumentation may increase the risk of urological infection.

Given the prevalence of bladder outlet obstruction from prostatic hyperplasia, nephrologists also require some understanding of basic pharmacologic therapies for this problem (Table 2). Other specific causes of uropathy which benefit from adjuvant medical therapy include retroperitoneal fibrosis, with immune-modulators, nephrolithiasis in the form of calcium channel blockers, and cancer through chemotherapy.

PROGNOSIS

The most important predictors of renal recovery are the completeness and duration of obstruction, and the presence or absence of coexisting infection. There is an inverse relationship between chronicity and reversibility; urinary tract obstruction for less than 1 wk is typically associated with complete recovery. The majority of patients experience complete recovery of kidney function with reversal of obstruction. Most improvement occurs in the first fortnight following decompression but ongoing renal recovery may be seen for up to 6 mo. High-grade obstructive uropathy for more than 6-8 wk is said to be irreversible. However, with good preventative care the trajectory of CKD related to obstructive uropathy tends to be benign with only 3% of patients progressing to dialysis at 10 years[22]. A significant minority of patients commenced on dialysis at the time of diagnosis gradually improve and are freed from dialysis after several months[7].

Total destruction of an infected obstructed kidney may occur within a matter of days. Without decompression the infected obstructed kidney is associated with a 40% mortality[30], compared to a mortality rate of less than 5% following successful decompression[31].

Positive prognostic features for renal recovery include POD, younger age, a normal pre-morbid GFR, and lower grades of hydronephrosis as opposed to higher[14,32]. Obstruction severity is more important for renal outcome than aetiology, though bladder outflow obstruction appears to yield a better prognosis than upper tract obstruction because vesical trabeculation and hypertrophy protect the renal parenchyma from a high-pressure system.

Although obstructive uropathy is associated with low short-term mortality, intermediate- and long-term outcomes are poor, particularly for those older than 85 years of age[5]. The median 12-mo survival for patients presenting with malignant and non-malignant obstruction is roughly 40% and 90%, respectively[22].

Table 2 Common perioperative considerations and medical therapies for obstructive uropathy

Medication class	Comments
Perioperative care	
Non-steroidal anti-inflammatory drugs	Should be avoided or used cautiously in any form of acute or chronic kidney disease There is ample experimental and clinical evidence suggesting that non-steroidal anti-inflammatory drugs (NSAIDs) may worsen kidney function in patients with renal impairment, especially during a concomitant physiologic insult, and delay renal recovery from acute kidney injury (AKI)[33-36]. NSAIDs interfere with renal auto-regulation and can directly induce <i>de novo</i> AKI through several mechanisms.
Antihypertensives	Hypertension is frequently seen in patients with obstructive uropathy, due to volume expansion and upregulation of renin and erythropoietin release because of focal hypoxia[37,38] Hypertension may reverse rapidly following acute relief of obstruction and diuresis, so antihypertensive medications should be rationalised accordingly Renin-angiotensin system blockade, with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, should be avoided or prescribed carefully due to the well-recognised risks of pre-renal AKI and hyperkalaemia
Antibiotics	Leucocytosis and raised inflammatory markers are commonly seen in acute presentations of urinary tract obstruction as part of the stress response. A low threshold for empiric antimicrobial coverage for urinary infection is prudent Renal drug clearance declines roughly in proportion to the drop in GFR. Antibiotic dosing or frequency may need to be reduced, depending on the agent. Antibiotics considered 'nephrotoxic' may need to be withheld, such as vancomycin and gentamicin Urosepsis in the context of an obstructed collecting system is tissue-invasive. Therefore, selected antibiotics must be broad-spectrum and penetrant, and reach therapeutic levels quickly. Intravenous ampicillin or ceftriaxone are typical choices, which can be modified based on culture sensitivities
Obstructive uropathy pharmacologic therapies	
Alpha-1 adrenergic receptor antagonists	Common uses: Benign prostatic hyperplasia, urolithiasis (medical expulsive therapy) Rationale: Induce smooth muscle relaxation, thereby enlarging ureteral and urethral calibre and improving flow Examples: Prazosin (non-selective), tamsulosin (selective), silodosin (selective)
5-alpha reductase inhibitors	Common uses: Benign prostatic hyperplasia Rationale: Targeted antiandrogen effect, thereby reducing prostate volume and the static component of bladder outlet obstruction Examples: Dutasteride, finasteride Combination tablets with alpha-1 adrenergic receptor antagonists are also widely available
Phosphodiesterase-5 inhibitors	Common uses: Benign prostatic hyperplasia, erectile dysfunction Rationale: Exact mechanism of action in lower urinary tract symptoms is unclear but may antagonise phosphodiesterase (PDE) receptors on smooth muscle cells, thus inducing urethral relaxation and improved urine flow, or increase bladder and prostate perfusion Examples: Sildenafil, tadalafil, vardenafil PDE-5 inhibitors are commonly prescribed for men with erectile dysfunction and coexisting features of prostatism. PDE-5 inhibitors may also be used in combination with alpha-1 adrenergic receptor antagonists or 5-alpha reductase inhibitors

TAKEAWAY POINTS

The therapeutic approach to obstructive uropathy is less well understood than in other forms of acute or chronic renal failure. A joint effort between urologists and physicians is necessary. Priorities include catheterisation and surgical correction of the underlying lesion.

An early post-decompression polyuric phase with electrolyte losses is common, requiring judicious monitoring and replacement. Although usually mild, post-obstructive diuresis may be a complex process that quickly transitions from volume overload to dehydration and an attentive fluid management protocol is warranted. Nephrologists should be particularly wary of evolving hypernatraemia, which must be treated urgently.

Many patients develop CKD and should receive long-term nephrology follow-up. Cardiovascular risk factor reduction is pertinent and evidence-based, including blood pressure control and use of ACE inhibitors and SGLT2 inhibitors for reno-protection. The kidney-specific prognosis is generally favourable with few patients proceeding to dialysis.

CONCLUSION

Obstructive uropathy is a potentially reversible condition. Surgical decompression of the urinary system is the key component of care, but many surrounding medical issues must also be considered. Most cases of obstructive uropathy experience complete renal recovery, but a significant minority develop chronic kidney disease or require dialysis. Patients therefore benefit from inter-speciality collaboration between urologists and nephrologists.

FOOTNOTES

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'Children Kidney Care Centers': Rationale, requirements and recommendations for best facilities and better future

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Abstract

Specialized centers are needed for nephrology and urology care of children. The justifications are the specialized nature of care needed and the growing incidence and prevalence. Children with chronic kidney disease (CKD) are at risk of morbidity, mortality, and decreased quality of life. Current pediatric practice structures are apparently poorly suited for the increasing demands of chronic disease in children. Kidney diseases account for around 8%-10% of total outpatients and 12% of admissions to the pediatric ward in hospitals. The major causes of pediatric CKD in registries are congenital anomalies of the kidney and urinary tract (around 50%), followed by inherited nephropathies and glomerulonephritis. The nephrologist's role is important for specialized investigations and treatment. Urologist's services are essential for the wide variety of conditions from birth to early adult age for complete cure and complementing medical management. Children have a right to treatments and to resources that are as sophisticated and advanced as those available to adults. Simple and sophisticated care for all children with ailments of the kidneys and related structures is important for ensuring 'health for all'. The availability of 'Child Kidney Care Centers' will go a long way in improving the lives of affected children.

Key Words: Chronic kidney disease; Congenital anomaly; Hereditary nephropathy; Glomerulonephritis; Nephrology; Urology

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Core Tip: Current pediatric practice structures are apparently poorly suited to meet the growing demands of chronic disease. Serious childhood morbidity and mortality can result from chronic disorders. Specialized centers provide the opportunity for systematic and focused delivery of high-quality clinical care in a sophisticated manner. An understanding of the etiology of chronic renal failure in children guides efforts and excellence goals. The availability of specialized investigations in a center is required, and will ensure prompt care, avoiding unnecessary referrals, which causes delays. ‘Children Kidney Care Centers’ will ensure correct treatments, both nephrology and urology, with sophistication for success.

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INTRODUCTION

Kidneys are important for maintaining the interior milieu and hence in children for ensuring growth, for preventing morbidity, and for obviating mortality all diseases of the kidneys need focused attention. The urinary system disorders and diseases spectrum is diverse and distinct, incidence is a cause for concern, investigations are specialized, and treatment specific and timely. Hence, the need for centers for nephrology and urology care for children and the necessity for review and recommendations. Also, it has been commented that current pediatric practice structures are not suitable in meeting the growing demands of chronic disease in children. All this points to the need for major reform in organization, financing, and training[1]. Specialized centers provide the opportunity for systematic and sophisticated focused delivery of high-quality clinical care[2]. Specialized care is often challenging but universal access to treatment services is possible with commitment[3]. ‘Children Kidney Care Centers’ will be an important step in the right direction.

The International Pediatric Nephrology Association (www.ipnaonline.org) role in enhancing knowledge and communication among pediatric nephrologists, aligned practitioners, and other health professionals has been critical on progress and praiseworthy[4]. Establishment of ‘Children Kidney Care Centers’ will go a long way in specialized practices with sophisticated protocols. All the latest research developments need to be put into proper perspective for practice and future developments.

The leading causes of global under-five year of age mortality rate are preterm birth complications (15.9%) and pneumonia (15.5%). The third largest is other causes (13.5%)[5,6]. It is high time that we also focus on these other causes. The evolving trend, as suggested by analysis in the past several decades, is that chronic disease prevalence has risen, and serious acute illness incidence in children has fallen. This has resulted in an increasing concentration of serious childhood morbidity and mortality due to chronic disorders[1]. Children with chronic kidney disease (CKD) are at risk of increased lifelong morbidity, mortality, and decreased quality of life[7].

The magnitude of CKD varies in different geographical areas. This is due to genetic and environmental factors. The major causes of pediatric CKD in registries are congenital anomalies of the kidney and urinary tract (UT) (approximately 50%), followed by the inherited nephropathies and glomerulonephritis[8]. In India, the true incidence and burden of CKD in children is not known, due to the lack of a national registry. In one of the Command Hospitals in India the work load of kidney disease in children is approximately 8%-10% of total outpatient attendance. This has accounted for 12% of admissions to the pediatric ward[9]. Alarming, it has been reported that 58% of children with renal failure presented with end stage renal disease (ESRD)[10]. Thus, prompt diagnosis and proper management is essential. Evidence shows that children fare better than adults if they receive kidney replacement therapy including dialysis and transplantation. Disparities in access to care exist. All this justifies effective efforts for children with kidney disease. These should be for all regions and including all economic strata[11]. These distinctive features justify dedicated facilities.

Similarly, statistics for the newborn period reveal that 0.8% of cases have abdominal masses, and renal origin masses account for the majority of these. The most common etiologies are: (1) Polycystic kidneys; (2) multicystic dysplastic kidney; (3) hydronephrosis; and (4) renal vein thrombosis. There is a need for specific and specialized management[12]. Thus, there is a need for focused committed comprehensive centers.

High quality systems of healthcare delivery require health leaders and managers with adaptable and relevant capabilities. This has been thought of as critical[13]. Our justifications given above based on epidemiological evidence and the importance of timely intervention point to the need for adaptation to establish ‘Children Kidney Care Centers’. Furthermore, relevant capabilities’ building requires understanding of the spectrum of illness, the specialized investigations, and the specific treatments. These are elaborated for sophisticated establishment and scientific execution.

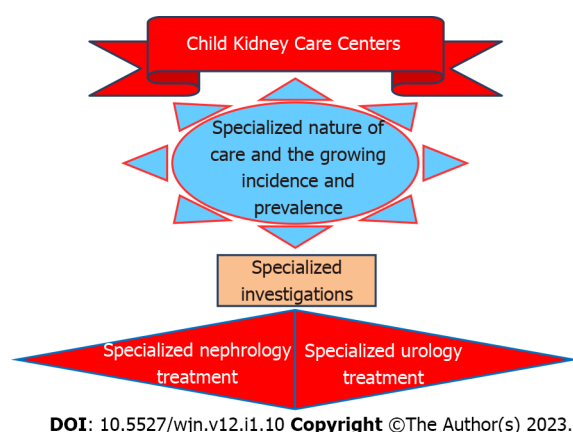


Figure 1 'Children Kidney Care Centers' need and necessary facilities.

Conceptual frameworks illuminate and magnify illustratively. These simplify ways of representing how complex things work. A conceptual framework pictorial representation for need and necessary facilities of 'Children Kidney Care Centers' is given at Figure 1.

SPECTRUM

In a study of the etiology of pediatric chronic renal failure (ages 0-18 years) the common causes reported are obstructive nephropathy (31.8%), chronic glomerulonephritis (27.5%), and reflux nephropathy (16.7%). The less common causes are hereditary nephropathy (7.5%), renal dysplasia (4.9%), neurogenic bladder (4.5%), and hemolytic uremic syndrome (1.6%)[14]. Pictorial depiction of various etiologies is given at Figure 2. All this guides efforts and excellence goals at 'Children Kidney Care Centers'.

Obstructive uropathy

Most childhood obstructive lesions are congenital. In a study of the etiology and burden of comorbidities across stages of CKD in children it was concluded that kidney and UT congenital anomalies were the commonest cause of CKD[15]. Common causes are posterior urethral valve, pelviureteric junction obstruction or hydronephrosis, and nephrolithiasis.

Glomerulonephritis

A common renal disorder and a leading cause of ESRD is glomerulonephritis[16,17]. Its presentations are protean. The general features include proteinuria, hematuria, renal failure, and hypertension. Early therapeutic intervention is warranted and leads to renal function improvements and long-term preservation of renal function. All this is required to prevent the progression to end-stage renal failure. Hence, early evaluation is important in appropriate centers.

Glomerulonephritis types presenting with recurrent hematuria are immunoglobulin A nephropathy (Berger nephropathy) and Alport syndrome. Membranoproliferative glomerulonephritis (also termed mesangiocapillary glomerulonephritis) most commonly occurs in children or young adults. The presentation is varied and includes: (1) Nephrotic syndrome; (2) acute nephritic syndrome (hematuria, hypertension, and some level of renal insufficiency); and (3) persistent asymptomatic microscopic hematuria and proteinuria. The presentation of rapidly progressive glomerulonephritis and crescentic glomerulonephritis in most children is acute nephritis (hematuria, some degree of renal insufficiency, and hypertension). These children usually have concomitant proteinuria, often with nephrotic syndrome. Other important presentations are systemic lupus erythematosus (SLE)-associated glomerulonephritis, Henoch-Schonlein purpura nephritis, and Goodpasture disease. A common cause of community acquired acute kidney injury in young children is hemolytic-uremic syndrome (HUS). The characteristic triad of HUS is: (1) Microangiopathic hemolytic anemia; (2) thrombocytopenia; and (3) renal insufficiency. Expert diagnosis and early treatment is especially suited in specialized centers.

Reflux nephropathy

Vesicoureteral reflux (VUR), the reverse flow of urine from the bladder to the ureter and kidney, is a risk for kidney infection (pyelonephritis). The reaction due to inflammation caused by pyelonephritis results in renal injury or scarring. Renal function is impaired with extensive renal scarring. This also leads to hypertension (renin-mediated), renal insufficiency/ESRD, and somatic growth impairment.

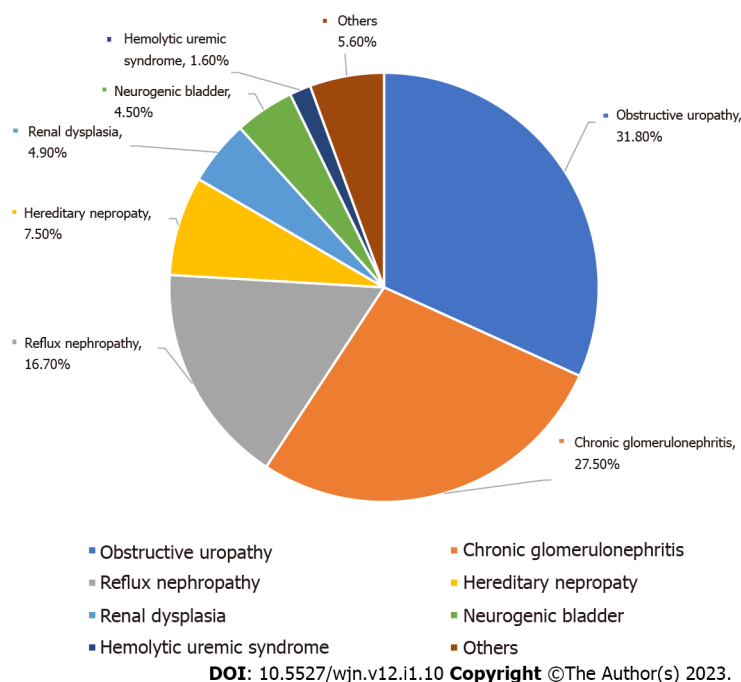


Figure 2 Chronic renal failure etiological spectrum.

SPECIALIZED INVESTIGATIONS

Kidney injury occurs due to a variety of different mechanisms. Investigations into the type of injury, the degree of injury and assessment of progression involve laboratory tests, diagnostic imaging, and often tissue sample studies. All investigations available in a specialized center are required, and 'Children Kidney Care Centers' can guarantee this. This will ensure prompt care and avoid unnecessary referrals, which causes delays. The best evidence-based practices are as follows.

Glomerular filtration rate

Glomerular filtration rate (GFR) is a measure of kidney function. The GFR can be measured optimally by the clearance of inulin. However, in clinical practice it is cumbersome. Hence, GFR estimation is commonly performed using the endogenous creatinine clearance test. The Schwartz formula is the most widely used bedside pediatric formula[18,19].

More recently, GFR estimation is assessed by cystatin C, an endogenous marker of renal function. This non-glycosylated protein is produced in all cells in relative constancy. The advantage of measuring cystatin C is that it is not influenced by age, gender, body habitus or composition[20].

Protein measurement

Proteinuria assessment for diagnosis, prognosis, and monitoring therapy response is carried out routinely. Proteinuria on urinalysis is often the first clue to renal injury. Subtle and early glomerular injury is identified by microalbuminuria measurements. Twenty-four-hour urinary protein is the gold standard for defining proteinuria. It has been largely replaced by the spot protein/creatinine ratio measurement in a random urine sample. This correlates to 24 h urine protein reasonably well[21].

Hematuria

Hematuria is a nonspecific finding. It indicates some injury, and does not provide more information. However, dysmorphic red blood cells (RBCs) study with phase contrast microscopy is useful for identifying the injury site in the UT. If 75% or more of the observed RBCs are dysmorphic, the site of injury is the kidney, and most likely the glomerulus. If less than 25% of the observed RBCs are dysmorphic, the injury site is the UT from the renal pelvis downwards[22].

Tubular function

The commonly used dynamic tests of tubular function are fractional calcium, phosphate or sodium excretion calculations. The general formula for calculations is: (urine concentration of analyte × serum creatinine)/(serum concentration of analyte × urinary creatinine). A very low fractional excretion of calcium indicates familial benign hypercalcemia. Increased fractional excretion of phosphate indicates hypophosphatemic rickets. Calculation of fractional excretion of sodium (FENa) is useful for differentiating volume depletion from acute tubular necrosis. In volume depletion, the tubules avidly conserve

sodium and FENa is typically less than 1.0. In acute tubular necrosis, the tubules are damaged and are less able to conserve sodium, and FENa is typically more than 1.0.

Facilities for measurement of 24 h excretion of solutes (calcium, phosphate, oxalate, uric acid, and dibasic amino acids) are useful in the diagnosis of renal stone disease. Twenty-four-hour collection is best, but random measurement of the urine calcium (mg/dL): Urine creatinine (mg/dL) ratio can be used in the diagnosis of hypercalciuria[23].

Immunology

The diagnosis of renal disease secondary to SLE is performed by anti-nuclear antibodies tests. These include antibodies to extractable nuclear antigens and the anti-double-stranded DNA antibodies. In glomerulonephritis secondary to systemic vasculitis, antineutrophil cytoplasmic antibodies detection aids diagnosis. In Goodpasture syndrome, antibodies to glomerular basement membrane are seen. Low levels of complement are seen in SLE, systemic vasculitis and HUS.

Complement level measurements are required for fixed proteinuria and glomerular hematuria initial evaluation.

DIAGNOSTIC IMAGING

Ultrasound

Ultrasound (US) for visualization of the UT is the principal imaging modality. For children US is advantageous. The use of transducers with high-frequency (7-11 MHz) and lower-frequency (3.5-5 MHz) is recommended. High frequency sound waves have less penetration, but provide greater resolution. Ideally one must use the maximum frequency that penetrates to the depth where study is required. As compared to large or obese individuals, high frequency US can be readily used in infants and small children producing excellent resolution.

Doppler US should be used for blood flow evaluation. It is useful in study of: (1) Renal artery disease; (2) renal vein thrombosis; (3) tumor thrombosis in the renal vein and inferior vena cava; and (4) arteriovenous fistula thrombosis. Power Doppler mode allows blood flow detection with increased sensitivity. It is better than color Doppler US. Power Doppler is useful in detecting intrarenal blood flow, and in identifying areas of decreased perfusion within the kidney. It should be utilized for detecting acute pyelonephritis[24].

US contrast imaging has many potential applications. These include: (1) Characterization of complex renal cysts; (2) assessment of renal vascular disorders, infection, and transplant kidneys; and (3) differentiation of complex renal cysts and solid lesions, and between renal pseudomasses and tumors[25].

Voiding cystourethrography

Voiding cystourethrography (VCUG) is the gold standard for the diagnosis of VUR. It is the only modality that detects VUR and gives detailed information on the bladder and urethra[26]. The use of pulsed fluoroscopy importantly reduces VCUG-radiation exposure side effects[27].

Intravenous pyelography

The availability of US and magnetic resonance urography has dramatically decreased the need for and use of intravenous pyelography (IVP)[28]. Bowel gas and immaturity of renal function in children often results in suboptimal IVP images. Also, IVP has risks of radiation and contrast exposure.

Antegrade pyelography

This is carried out with percutaneous nephrostomy tube insertion and contrast agent injection. The indications are nephrostomy tube placement to drain an obstructed infected kidney or to provide percutaneous nephrolithotomy access. In cases in which retrograde studies are prevented by obstruction at the extreme lower end of the ureter, antegrade pyelography is useful.

Computed tomography

Excellent anatomic resolution of the UT is provided by computed tomography (CT). Thin-section helical imaging (spiral CT scan) gives multiplanar reformatted images quickly. Its uses include: (1) Initial evaluation of possible symptomatic nephrolithiasis, as a preferred modality; and (2) diagnosis of suspected trauma of the UT, as the optimal modality. It is useful for renal tumor staging. Assessment of renal artery stenosis is carried using CT angiography.

Magnetic resonance imaging

The advantages of magnetic resonance imaging (MRI) are: (1) Multiple plane images; (2) excellent resolution; and (3) good distinction between different tissue types. All this is without radiation exposure. As compared to iodinated contrast studies, gadolinium-based contrast studies at standard doses are significantly less nephrotoxic. However, when gadolinium-based contrast is used at

radiographic doses for angiographic procedures it is nephrotoxic[29,30]. MRI is valuable in assessing congenital abnormalities.

Nuclear medicine

Nuclear medicine imaging provides accurate evaluation of renal function and useful renal imaging in many clinical situations. The requirements are radiotracers (radio-pharmaceuticals) and a scintillation detector/gamma camera. Exposure to radiation occurs, but is less compared to other modalities such as VCUG, IVP, or CT.

Dynamic renal scintigraphy is performed for functional information. This is carried out using mercaptoacetyl triglycine labelled with technetium ($^{99m}\text{Tc-MAG}_3$). For most indications, $^{99m}\text{Tc-MAG}_3$ is better than $^{99m}\text{Tc-DTPA}$. This is due to rapid excretion of $^{99m}\text{Tc-MAG}_3$ hence providing a superior renal/background ratio. A $^{99m}\text{Tc-MAG}_3$ scan provides information on the perfusion of each kidney, which is valuable in various clinical settings. It is useful in diagnosis when collecting system dilatation is caused by obstruction. In cases with significant obstruction of the outflow tract, $^{99m}\text{Tc-MAG}_3$ persists in the renal pelvis and a loop diuretic fails to accelerate its descent (diuresis scintigraphy). The functional significance of a 'baggy' or equivocally obstructed collecting system is distinguished, without undertaking pyelography.

Static renal scintigraphy is used for structural information. This uses dimercaptosuccinic acid labelled with technetium ($^{99m}\text{Tc-DMSA}$). It has the property of being taken up by proximal tubular cells. The intravenous injection is followed by the renal cortex images captured. These show the shape, size and relative function of each kidney. The method is sensitive in demonstrating cortical scarring in reflux nephropathy and is thus a way of assessing the function of each kidney individually. It usefully quantifies the amount of renal cortex in patients with renal dysplasia and hypoplasia.

Endoscopy

Small caliber flexible fiberoptic cystoscopes are useful in diagnostic cystourethroscopy, and retrograde ureterography. Posterior urethral valves are definitively diagnosed using endoscopy.

Urodynamic studies

Investigations for urinary incontinence or other urinary symptoms are required to make a definitive, objective diagnosis. A Cochrane review had concluded that "While urodynamic tests have been found to change clinical decision making, there is also some evidence that this does not result in better outcomes, as urinary incontinence rates difference after treatment"[31]. For further research to achieve better outcomes, special facilities can play an important role.

Urodynamic studies evaluate parameters of filling and emptying of the lower urinary tract. The bladder is filled with either water, or carbon dioxide while monitoring the pressure in the bladder (*via* bladder catheter) and in the abdomen (*via* rectal balloon). Simultaneously, the pelvic floor electromyography activity is measured by needle or surface electrodes placed in the perineum. The study is often carried out with fluoroscopy—"the video urodynamics". This is done to obtain information on the appearance of the bladder wall, presence/absence of VUR, emptying efficiency, and most importantly, the bladder neck and urethra appearance, along with their respective pressure recording for evaluation. The anatomy and physiology of the lower urinary tract requires careful performance with proper patient cooperation. The latter, being the limiting factor in its use in the evaluation of children.

A noninvasive urodynamics study involves: (1) Voided volume measurement; and (2) flow pattern assessment with a flowmeter. Essential information gathered is displayed graphically, and includes: (1) The measured urine flow rate; (2) urine volume voided along the shape of the voiding curve; and (3) the maximum flow rate. US is used for determination of post-void residual urine volume.

Kidney biopsy

The facilities for kidney biopsy are desirable. The most commonly used method is percutaneous renal biopsy. Automatic spring-loaded biopsy systems are now used, as the technique is simple and easy to use[32,33]. Biopsy examination requires special light microscopy, immunofluorescence techniques, and electron microscopy providing the most accurate diagnosis.

In the transplant setting, fine-needle aspiration biopsy is most often used for the analysis of immunologically activated cells. As this is less invasive, it is useful for possible serial monitoring of interstitial cellular infiltrates in transplanted kidneys[34].

SPECIFIC TREATMENTS

Children should have access to treatments and resources that are as sophisticated and advanced as those available to adults. Pediatricians, pediatric nephrologists, and pediatric urologists are integral in 'Children Kidney Care Centers'. The multi-disciplinary teams required for comprehensive care provision in children with kidney disease and their families are: geneticists, genetic counselors, nurse

specialists, dialysis personnel, nutritionists, social workers, and mental health professionals. All these professionals under one roof is desirable. A regular supply of all consumables needed should be ensured. All medicines including immunomodulatory drugs should be readily available. Relevant clinical practice guidelines are an important component of specialized centers. The facilities, features, and functioning in 'Child Kidney Care Centers' are discussed below.

Dialysis

The choice of dialysis modality to manage a specific patient is influenced by several factors. These are: (1) The goals of dialysis; (2) the unique advantages and disadvantages of each modality; and (3) institutional resources[35]. The last factor should not limit the management of these important conditions.

In the United States, peritoneal dialysis (PD) continues to be the most utilized dialysis modality (~55%) as compared with hemodialysis (~44%). However, hemodialysis (HD) as the initial maintenance dialysis therapy is being increasingly utilized. In the selection of dialysis modality age is a defining factor. In the age group from birth to 5 years of age maintenance dialysis treatment using PD is preferred (85%). In children ≥ 13 years of age initiation of maintenance dialysis treatment with HD is common (50%)[36].

There are some universal rules for the choice of dialysis modality: (1) HD avoidance in infants due to difficulties with vascular access; and (2) HD use when PD cannot be used due to technique failure, intra-abdominal pathology, or social difficulties.

PD

PD is preferred and is a convenient treatment modality for acute kidney injury (AKI) and patients with hemodynamically instability[37]. There is a recent trend towards increased continuous renal replacement therapy (CRRT) utilization vis-à-vis peritoneal dialysis for treating pediatric AKI. PD is still the most common modality used in children younger than 6 years of age[38].

The cornerstone of successful PD is a reliable peritoneal catheter. The PD catheters made of soft material (silicon rubber or polyurethane) are suitable for long-term placement. A number of dialysate transfer sets and associated devices have been developed to reduce the risk of bacterial contamination during either the catheter-to-transfer set or the transfer set-to-dialysate bag connections. This has contributed to simplifying PD connecting maneuvers[39].

Second generation PD solutions are more biocompatible. For standard nighttime automated PD, the neutral pH bicarbonate/lactate-buffered solution is used. For a long daytime dwell, the solution used is icodextrin. For malnourished patients, an amino acid-based solution is used. These solutions are safe and effective[40].

For patients with ESRD, PD can provide continuous ambulatory peritoneal dialysis and automated therapy using a cycler (continuous cyclic peritoneal dialysis/intermittent peritoneal dialysis/nocturnal intermittent peritoneal dialysis).

HD

Intermittent HD is useful in children with a relatively stable hemodynamic status. Pediatric HD machines with specific features for children need to be provided. These are useful as they have low blood flow speed capability and can function with lines of varying blood volumes. With the capability to measure and remove very small amounts of fluid these are suitable even for infants. The volumetric fluid removal system allows accurate fluid removal. New machines have advanced systems for continuous online monitoring and automatically adjust parameters using a biofeedback system.

Incorporation of the online hemodiafiltration (OL-HDF) module into the dialysis proportioning machine hardware makes the handling procedure simple. It secures the process by maintaining the safety regulation of the monitor. This has the advantage of virtually unlimited amounts of sterile and nonpyrogenic substitutive solution[41]. Incorporating OL-HDF in the RRT of children is beneficial, and improves most of the clinical and laboratory parameters measured[42].

The crucial factor for success of dialysis is good vascular access. The best form of access is an arterio-venous (a-v) fistula. Otherwise a line that is tunneled subcutaneously is used, or shunts/grafts may rarely be required[43]. Tunneled subcutaneous lines are used in: (1) Children too young for an a-v fistula; and (2) children not expected to be on dialysis long-term *e.g.* children awaiting a living related transplant.

CRRT is advantageous in patients with: (1) Unstable hemodynamic status; (2) concomitant sepsis; and (3) multiorgan failure in the intensive care setting. CRRT can be performed as: (1) Continuous venovenous hemofiltration; (2) continuous venovenous hemofiltration dialysis; and (3) continuous hemodiafiltration. Modern CRRT machines are very user-friendly, and with computer modules from which physicians can choose the CRRT modality[44].

Wearable and implantable artificial kidneys are the future of hemodialysis, and should be designed specifically for children.

Interventional nephrology

The interventions assuming importance and impacting advantageously are insertion of tunneled

hemodialysis and peritoneal dialysis catheters, endovascular procedures, percutaneous nephrostomy, ureteral stent placement, *etc.*

UROLOGY

Urologist's services are essential for a wide variety of conditions from birth to early adult age for complete cure and complementing medical management. The specialized management that should be available in the 'Child Kidney Care Centers' is discussed below.

Obstructions of the urinary tract

Ureteropelvic junction obstruction: Correction of this anomaly requires pyeloplasty. The success rate ranges from 91% to 98%. Pyeloplasty can be carried out using laparoscopic techniques, and is often robot-assisted using the da Vinci robot. Surgery conducted by surgical robots has the advantages of: (1) Small incision; (2) very minimal blood loss; (3) quick recovery; (4) shorter hospital stay; and (5) faster return to normal life. The advantages for the surgeon are: (1) A magnified, high-definition, three-dimensional view; and (2) tiny surgical instruments for manipulation, that have better flexibility than human hands.

Posterior urethral valves: Definitive treatment is performed by destruction of the valves endoscopically. Continuing supportive treatment is required for: (1) Dilated urinary tract; (2) recurrent urinary infections; and (3) uremia.

Other conditions for which surgery may be required are an ectopic ureter, ureterocele, megaureter, *etc.*

Urolithiasis

Calculus removal is necessary if: (1) The calculus does not pass; (2) seems unlikely to pass; and (3) if there is associated urinary tract infection. Lithotripsy of bladder, ureteral, and small renal pelvic calculi can be done using the holmium laser through a flexible or rigid ureteroscope. This is quite effective. Extracorporeal shock wave lithotripsy is the other option, and can be used in children with renal and ureteral stones. This has a success rate of more than 75%. Percutaneous nephrostolithotomy is another alternative. In this where the renal collecting system is accessed percutaneously, and breaking of the calculi is carried out using ultrasonic lithotripsy. If these modalities are unsuccessful, laparoscopic removal is an alternative. The da Vinci robot can be utilized for this procedure.

Vesico-ureteric reflux

Surgery is needed to minimize the risks of ongoing VUR. Nonsurgical therapy is required for infection prophylaxis and follow-up testing. VUR correction options include: (1) Lower abdominal or inguinal incision (open); (2) laparoscopically (with or without robotic assistance); and (3) endoscopically with sub-ureteral injection.

Neuropathic bladder

Reconstructive urinary tract surgery is needed in cases of incontinence persisting despite medical therapy. This can almost always provide complete or satisfactory continence.

The two indications and comprehensive treatments are as follows.

Low urethral resistance: bladder neck reconstructive procedures (such as a periurethral sling) are often successful. Alternatively, an artificial sphincter implantation is usually successful. The components used in this technique are: (1) An inflatable cuff placed around the bladder neck; (2) a pressure-regulating balloon implanted in the extraperitoneal space; and (3) pumping mechanism implanted in the scrotum of boys and in the labia majora of girls.

Low bladder capacity or compliance, or persistent uninhibited contractions despite anticholinergic therapy: enlargement of the bladder with a patch of small or large intestine, termed augmentation cystoplasty or enterocystoplasty, is effective. Following this there is still a need to perform clean intermittent catheterization. If there is difficulty in urethral catheterization, a continent urinary stoma may be incorporated into the urinary tract reconstruction. The Mitrofanoff procedure is a useful and commonly performed technique. During this procedure, the appendix is isolated from the cecum on its vascular pedicle and is interposed between the bladder and abdominal wall. This is done to allow intermittent catheterization through a dry stoma.

Hypospadias

The indications for surgery are: (1) To improve sexual function; (2) to correct problems with the urinary stream; and (3) for cosmetic reasons. The plastic surgical procedures used correct the chordee and re-site the urethral opening. The available procedures are: (1) Meatal advancement and glanuloplasty repair; (2) transverse island flap repair; and (3) island tube repair.

Except for proximal hypospadias, all cases are repaired in a single operation on an ambulatory basis. Proximal hypospadias may require a 2-stage repair.

Renal transplant

This is the optimal therapy for children with ESRD. Survival rates with kidney transplantation are better than hemodialysis or peritoneal dialysis. Children and adolescents with ESRD require a renal transplant more than adults. This is justified in order to achieve normal growth and cognitive development. Successful transplantation leads to: (1) Improvement in linear growth; (2) possible school attendance; and (3) freedom from dietary restrictions.

Future directions

Pediatric Centers of Excellence in Nephrology are needed and the National Institutes of Health is promoting these centers. Grants are provided for accelerating basic, translational and clinical research in pediatric kidney disease. Important research being funded for pediatric patients include: (1) CKD in Children study; (2) Nephrotic Syndrome Study Network; (3) Cure Glomerulonephropathy; and (4) Polycystic Kidney Disease Research Resource Consortium.

Basic science research projects include: (1) The (Re) Building a Kidney Consortium; (2) the GenitoUrinary Development Molecular Anatomy Project; and (3) the Kidney Precision Medicine Project. All this is inspiring the pediatric nephrology research community. Progress has been made in molecular and genetic analyses. Specific gene products have been linked to normal and abnormal kidney growth and development causation in a few human pediatric kidney diseases. It has been commented that much remains to be explored. The future is exciting.

CONCLUSION

Health for all should include all children with disorders of the kidneys and related structures. The availability of 'Child Kidney Care Centers' will go a long way in improving the lives of affected children. Pertinent and professional care, both simple and sophisticated is likely to reap rewards. Strategies suggested for focused attention and favorable actions can lead to success, happiness and health.

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Kidney stone matrix proteins: Role in stone formation

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Abstract

Stone formation is induced by an increased level of urine crystallization promoters and reduced levels of its inhibitors. Crystallization inhibitors include citrate, magnesium, zinc, and organic compounds such as glycosaminoglycans. In the urine, there are various proteins, such as uromodulin (Tamm-Horsfall protein), calgranulin, osteopontin, bikunin, and nephrocalcin, that are present in the stone matrix. The presence of several carboxyl groups in these macromolecules reduces calcium oxalate monohydrate crystal adhesion to the urinary epithelium and could potentially protect against lithiasis. Proteins are the most abundant component of kidney stone matrix, and their presence may reflect the process of stone formation. Many recent studies have explored the proteomics of urinary stones. Among the stone matrix proteins, the most frequently identified were uromodulin, S100 proteins (calgranulins A and B), osteopontin, and several other proteins typically engaged in inflammation and immune response. The normal level and structure of these macromolecules may constitute protection against calcium salt formation. Paradoxically, most of them may act as both promoters and inhibitors depending on circumstances. Many of these proteins have other functions in modulating oxidative stress, immune function, and inflammation that could also influence stone formation. Yet, the role of these kidney stone matrix proteins needs to be established through more studies comparing urinary stone proteomics between stone formers and non-stone formers.

Key Words: Stone formation; Kidney stone; Matrix proteins; Uromodulin; Calgranulin; Proteomics

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Core Tip: Several urinary proteins have been found in kidney stone matrix. *In vitro* and *in vivo* studies have shown that they have an important role in various processes of calcium oxalate crystallization. Many of them have other functions in modulating oxidative stress, immune response, and inflammation that could also influence stone formation. Yet, the exact role of these kidney stone matrix proteins needs to be established through more studies comparing urinary stone proteomics between stone formers and non-stone formers.

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INTRODUCTION

Healthy people regularly excrete calcium oxalate crystals in urine. Calcium oxalate stones are formed only in a small part of the population[1]. Stones develop from crystals that form in the urine, which contains a mixture of ions, salts, macromolecules, and metabolites[2]. Crystals undergo different stages (nucleation, growth, and aggregation) until they produce a stone.

Induction of stone formation is produced by an increased level of crystallization promoters in the urine and reduced levels of its inhibitors[3]. Crystallization promoters are those substances that may constitute the crystals by which stones are formed, in particular calcium and oxalate. Idiopathic hypercalciuria is probably the principal condition underlying stone formation that produces increased levels of urinary calcium[4]. Crystallization inhibitors include citrate, magnesium, zinc, and organic compounds produced by renal tubular epithelial cells as glycosaminoglycans. Several proteins, such as uromodulin [UMOD; Tamm-Horsfall protein (THP)], calgranulin, osteopontin (OPN), bikunin, and nephrocalcin (NC), are present in the urine[5]. These proteins that are frequently found in the kidney stone matrix will be the subject of this review (Table 1).

MACROMOLECULES AND CRYSTALLIZATION

We do not know the exact role of many macromolecules present in urine in calcium salt crystallization. The normal level and structure of these macromolecules may constitute protection against formation of large, intratubular precipitates of calcium salts. Paradoxically, most of them may act as both promoters and inhibitors depending on circumstances (for example urine pH).

Back in the 1970's, Gill *et al*[7] showed an inhibitory effect of macromolecules from human urine on crystallization of calcium oxalate[6]. The presence of several carboxyl groups in these macromolecules reduces calcium oxalate monohydrate crystal adhesion to the urinary epithelium[7]. The findings showed that macromolecules could potentially protect against lithiasis and that affected patients with lithiasis may have a different composition from that in healthy subjects.

Among macromolecules, proteins are present in all stones in a slight proportion, commonly < 5%. Several proteins rich in the urine proteome, have been examined in relation to their possible role in renal lithiasis. The most abundant component of kidney stone matrix are proteins, and their presence indirectly shows the process of stone formation. Urinary stones proteomics has been analyzed in several studies[5,8-10]. In a recent study, Kaneko *et al*[11] conducted a bioinformatic research on the proteomics of urinary stones to identify the most frequent stone matrix proteins present and afterwards performed immunohistochemistry to detect the top five of those matrix proteins expressed in renal tissue. Among the stone matrix proteins, the most frequently identified were UMOD, S100 proteins (calgranulins A and B), OPN, and several other proteins that participate in inflammation and immune response. Several proteins determined by immunohistochemistry in kidney stones showed increased expression, such as S100A8, S100A9 (calgranulins A and B), and OPN, while others such as UMOD decreased. Proteomic analysis of exosomes from kidney stone patients also showed higher expression of S100 proteins[12] while they were difficult to detect in urine.

Uromodulin

UMOD, originally known as THP, is a kidney-specific protein synthesized at the thick ascending limb of the loop of Henle[13,14]. Nearly 100 mg of this protein is excreted daily, and it is the most abundant of all urinary proteins. UMOD is a complex protein with several domains including a zona pellucida domain, essential for protein polymerization, and a special anchoring domain[15]. It is composed of 640 amino acids with 48 cysteine residues that form 24 disulphide bonds and glycosylation accounts for

Table 1 Kidney stone matrix proteins as modulators of crystallization

Matrix protein name	Primary function	Celular origin	Secondary function	Mol. weight (KDal)
Uromodulin	Inhibits crystal aggregation	Epithelial cells of the TALH	Reduces local oxidative stress	87
Calgranulins	Inhibit crystal growth and aggregation	Cells of myeloid origin	Participate in innate immuneresponse	10.9-13.2
Osteopontin	Inhibits/Enhances crystal formation and aggregation	Distal tubular epithelial cells	Regulator of immune response	14
Bikunin	Inhibits crystal nucleation, growth, and aggregation	Proximal tubules and the thin descending segment	Inhibition of the action of many serine proteinases	39
Nephrocalcin	Inhibit crystal nucleation, growth, and aggregation	Proximal tubule epithelial cells and TALH	None	18

TALH: Thick ascending limb of Henle.

nearly 30% of its molecular weight. UMOD monomers are produced by epithelial cells present in the thick ascending limb of the Henle loop and then transported and secreted at both cell surfaces. At the apical surface, it is cleaved and released to the tubular fluid. Polymerization occurs depending on the physiological conditions in the urine. Putative functions of this protein include the modulation of salt and water transport, prevention of kidney stone formation by binding calcium oxalate crystals, and defense against urinary tract infection[15]. The role of UMOD in health and disease has been provided by the study of genetic diseases caused by mutations in the *UMOD* gene[16].

Measurements of THP in kidney stone formers and healthy subjects have shown decreased urinary THP in stone formers[17,18]. Urinary excretion of calcium and oxalate ions positively correlates with urinary THP in controls but not in stone formers. Only calcium stone formers show a reduction in THP. More recently, Fraser *et al*[19] studied UMOD level in urine of children with stone disease. They did not observe differences in concentration of the protein excreted between the group with symptomatic lithiasis, the group endangered with lithiasis, and the control group. In another study in children, those with lithiasis had increased UMOD excretion[20]. Similarly, increased excretion of this protein, with its different composition at the same time, was observed by Jaggi *et al*[21] in urine of affected adults with high intensity of stone formation. Possible determinants of urinary THP excretion in kidney stone formers and control subjects were studied by Glauser *et al*[22], assessing 24-h THP excretion and expressing results in the form of THP/creatinine ratio. They found that in both controls and stone formers, urinary THP excretion was related to body size, renal function, and urinary citrate excretion, whereas THP excretion was not correlated with age, urine volume, or dietary habits (dietary calcium supply or protein consumption). An increase in THP in response to increasing urinary calcium and oxalate concentrations was seen only in controls, whereas this self-protective mechanism was absent in stone formers. Therefore, the different publications presenting quantitative differences in UMOD excretion did not have the same findings, which may indicate a random nature of the differences.

Other authors have found that UMOD structure is different between persons with and without kidney stones. Stone formers had lower protein content (32%), sialic acid content (27%), and amino sugar content (nearly 20%)[23]. Viswanathan *et al*[24] have shown that UMOD contains less sialic acid in patients with lithiasis, which leads to reduction of its negative charge. This form of protein promotes aggregation of calcium oxalate monohydrate, whereas the same protein prevents aggregation in healthy subjects with a normal content of sialic residues. Thus, not only UMOD levels but also differences in THP biochemical structure may influence the development of calcium nephrolithiasis.

To better understand the *in vivo* role of THP in kidney stone formation, Mo *et al*[25] inactivated the *THP* gene[25]. The resultant *THP*^{-/-} mice had no THP expression in the kidney. Intratubular crystal aggregates were seen in the collecting ducts at the inner medulla and renal papillae in these mice, while wild type littermates had no crystal deposition in the kidney. This papillary interstitial calcinosis of the *THP*^{-/-} mice is very similar to Randall's plaques seen in calcium oxalate stone formers, but ureteral stones have been found in this model[26].

Reactive oxygen species (ROS) and inflammation have a critical role in the pathogenesis of kidney stones[27]. ROS production increases when renal tubular cells are exposed to different type of crystals, leading to epithelial cell injury[28] and release of inflammatory mediators[29]. *THP*^{-/-} mouse kidneys have increased ROS accumulation in the kidney, particularly in the S3 segment of the proximal tubules [30]. Targeted proteomic analysis on S3 proximal epithelial cells in these mice showed that free radical scavenging proteins were at the top of the proteins that were differentially downregulated in *THP*^{-/-} mice[30]. Thus, it is possible that one of the mechanisms by which UMOD prevents renal lithiasis is through reducing local oxidative stress.

S100 proteins (calgranulins)

S100 proteins constitute a family of calcium-binding proteins present in the cytosol, characterized by their dissolution in 100% ammonium sulphate[31]. Several of them have been classified as danger-associated molecular patterns (DAMPs) of endogenous origin, including S100A7[32], S100A8, S100A9, and S100A12[31,33]. DAMPs, also known as alarmins, are a group of endogenous intracellular molecules characterized by multiple functions, and they are generally released as inflammatory signal mediators after cell death[34].

S100A8 and S100A9 are also known as calgranulins A and B, respectively. They are constitutively expressed and produced by cells of myeloid origin, such as neutrophils and monocytes[35], and dendritic cells[36]. In other cell types, they can be induced upon activation. S100A8 and S100A9 constitute nearly half of all cytosolic proteins in neutrophils, but only 1% in monocytes[35]. S100A8 and S100A9 in the presence of zinc and calcium ions form a heterodimer called calprotectin that promotes phagocyte migration by polymerization and stabilization of tubulin microfilaments in a calcium dependent manner[37].

Toll-like receptor 4 (TLR4) and RAGE (the receptor for advanced glycation end products) are thought to be the innate immune receptors of calgranulin[38,39]. Upon binding, TLR4 signaling is triggered, which is mediated by MyD88, thus leading to NF- κ B activation and secretion of pro-inflammatory cytokines[40,41]. Interaction of calgranulin with TLR4 has been shown to be involved in the pathogenesis of autoimmune diseases, systemic infections, malignancy, and acute coronary syndrome[42-45].

Momohara *et al*[46] showed the ability of calgranulins to inhibit crystallization, aggregation, and adhesion to the urinary epithelium of calcium oxalate monohydrate crystals. Mushtaq *et al*[47] also observed the presence of calgranulin in CaOx deposits but it promoted crystal aggregation. Bergsland *et al*[48] observed that the concentration and composition of calgranulin differed in subjects with a family history of urinary tract lithiasis in comparison with a healthy population. In children with stone disease, no statistically significant difference in calgranulin urine concentrations was observed between the study and control groups.

Osteopontin

OPN, also known as secreted phosphoprotein 1 (SPP-1), is a highly phosphorylated, strongly anionic glycoprophosphoprotein, with a molecular weight that ranges between 41 and 75 kDa, composed of 314 amino acids[49,50]. OPN was originally discovered in bone, as a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family of proteins, implicated in bone mineralization and remodeling[51]. OPN suffers multiple post-translational changes that modify the OPN responses in several tissues[50,52].

In addition to bone metabolism, OPN can regulate the immune response through interactions with multiple surface proteins localized in its target cells: Macrophages, dendritic cells, and T cells. Indeed, this protein has chemotactic properties on these cells[50]. Integrin receptor binding to OPN activates the intracellular nuclear factor kappa B (NF- κ B)[53]. OPN is also able to stimulate T-cell chemotaxis and adhesion, and it inhibits interleukin (IL)-10 release by macrophages[53]. In the kidney, OPN is produced and secreted into the urine by distal tubular renal epithelial cells, becoming a normal macromolecular constituent of the kidney[54].

Multiple observations support the concept that OPN may play an important role in modulating renal stone formation, such as: (1) OPN is one of the protein components of renal stone matrix[11]; (2) OPN can regulate the renal calcification process[55]; (3) OPN renal expression is altered in hyperoxaluric rats and urinary levels are changed in human subjects with urolithiasis[56]; (4) *In vitro* cell culture based studies and *in vivo* OPN knockout animal models suggest an important role of OPN in various phases of renal stone formation[57-59]; and (5) OPN polymorphisms have shown association with urolithiasis in different ethnic groups in candidate gene association studies[60,61].

Bikunin

Bikunin is a small chondroitin sulfate proteoglycan with a single glycosaminoglycan chain. It is the light chain of inter-alpha-inhibitor known for its inhibition of the action of many serine proteinases like trypsin and chymotrypsin. It exhibits a strong calcium oxalate crystal nucleation and aggregation inhibitory activity[62]. Immunohistochemical studies have shown that bikunin is localized in proximal tubules and the thin descending segment of the loop of Henle. It is absent in the glomeruli, distal tubules, or collecting ducts[63]. In subjects with lithiasis, bikunin does not prevent crystallization so well as in healthy subjects[64]. In a study by Médétognon-Benissan *et al*[65], strong inhibitory effect of bikunin on CaOx crystallization was confirmed by *in vitro* studies. On the other hand, a comparison of this protein in urine of adults with calcium oxalate lithiasis with urine of healthy subjects by means of the ELISA method, confirmed that bikunin level was 50% lower in affected subjects. On the contrary, a statistically significantly higher excretion of this protein in urine was observed in children with lithiasis [48].

Nephrocalcin

NC was the first urinary protein found to have crystal inhibitory properties[66]. This is a 14-kDa glycoprotein. It is a very potent inhibitor, compared to THP and OPN, the two other inhibitors, and is probably of major importance in protecting the kidneys against urinary supersaturation. NC contains γ -carboxyglutamic acid and has been shown to inhibit crystal growth, nucleation, and aggregation. The absence of γ -carboxyglutamic acid in the NC molecule from stone forming patients reduces its ability to inhibit nucleation and growth of calcium oxalate crystals[66,67].

To date, four isoforms of NC in urine have been reported. NC A and B isoforms are strong inhibitors, and C and D isoforms act as promoters for kidney stones[68].

A fifth NC was identified, called NC-PreA found in patients with renal cell carcinoma and in calcium oxalate renal extractions. In a recent study in children, Noyan *et al*[69] included 41 boys and girls with urinary stones and 25 age- and sex-matched healthy controls. The NC-PreA/creatinine ratio is significantly higher in patients with renal stones than in controls. This finding observed in stone-forming patients indicates that this ratio, too, may also be an important stimulatory molecule for urinary stone disease.

CONCLUSION

Despite many studies that have explored the proteomics of urinary stones, we still do not know the exact role of many of these matrix proteins found in kidney stones in calcium salt crystallization. The invariable presence of proteins in stones matrix raises the possibility that they play a role in stone formation, like the role that proteins have in healthy biomineralization. Are they protective molecules that were overwhelmed by mineral supersaturation? Can mineralization be promoted by these proteins? Are they merely a response to the disease process, including oxidative stress and inflammation? More studies are needed comparing urinary stone proteomics between stone formers and non-stone formers to elucidate the role of stone matrix proteins in stone formation.

FOOTNOTES

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Point of care ultrasonography in onco-nephrology: A stride toward better physical examination

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Abstract

Onco-Nephrology is an emerging subspecialty of Nephrology that focuses on a broad spectrum of renal disorders that can arise in patients with cancer. It encompasses acute kidney injury (AKI), complex fluid, electrolyte, and acid-base disorders, as well as chronic kidney disease caused or exacerbated by cancer and/or its treatment. In many such scenarios including AKI and hyponatremia, objective evaluation of hemodynamics is vital for appropriate management. Point of care ultrasonography (POCUS) is a limited ultrasound exam performed at the bedside and interpreted by the treating physician intended to answer focused clinical questions and guide therapy. Compared to conventional physical examination, POCUS offers substantially higher diagnostic accuracy for various structural and hemodynamic derangements. In this narrative review, we provide an overview of the utility of POCUS enhanced physical examination for the Onconeurologist supported by the current evidence and our experience-based opinion.

Key Words: Point of care ultrasonography; Onco-nephrology; Acute kidney injury; Hyponatremia; Volume assessment

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Core Tip: Point of care ultrasonography is a valuable adjunct to physical examination in patients with cancer and renal dysfunction or fluid/electrolyte disorders. It provides better diagnostic accuracy than conventional physical examination. Proper training is the key to effectively integrate this diagnostic tool into routine clinical practice.

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INTRODUCTION

Point of care ultrasonography (POCUS) is a focused ultrasound examination performed by the clinician at the bedside to guide patient management[1]. Recent years have witnessed a swift uptake of POCUS in almost all the clinical specialties and several medical schools have started teaching this skill to their students. According to a 2020 survey, 57% of the responding United States medical schools (69 out of 122) integrated POCUS instruction into undergraduate medical curriculum[2]. Once confined to procedural guidance such as dialysis catheter placement, the scope of POCUS in nephrology has now greatly expanded to include a wide array of diagnostic applications ranging from kidney ultrasound to focused echocardiography[3,4]. Some nephrology fellowship programs have even incorporated detailed hemodynamic monitoring using advanced Doppler techniques into their curricula[5]. **Figure 1** illustrates the sonographic applications that can be performed by nephrologists trained in POCUS. We have also seen in these past few years the emergence of Onco-Nephrology as a subspecialty within Nephrology[6,7]. This field focuses on management of kidney disorders in patients who have an active malignancy and are undergoing treatment for this. The breadth of kidney disorders seen and addressed in Onco-Nephrology practice includes acute kidney injury, hypertension, proteinuria, chronic kidney disease, fluid and electrolyte disorders to name a few. This article seeks to discuss the role and potential of POCUS in positively impacting the clinical practice of Onco-Nephrology by providing a few representative clinical scenarios.

THE RATIONALE FOR POCUS ENHANCED PHYSICAL EXAMINATION

Unlike a consultative ultrasound study which is expected to image an entire area in question (*e.g.*, abdominal ultrasound) with documentation of predefined measurements and parameters, POCUS is intended to answer focused questions that either narrow the differential diagnosis or provide a final diagnosis when interpreted in conjunction with history and physical examination by the treating physician. Moreover, it allows monitoring of a particular parameter in response to therapy without having to repeat the whole comprehensive study. For example, a nephrologist can follow a patient with uremic pericardial effusion in the outpatient dialysis unit with serial POCUS exams thereby avoiding repeated trips of the patient to the echocardiography laboratory. It is analogous to using a stethoscope (*point of care device*) to listen to heart and lung sounds, which is why some authors describe POCUS as a fifth pillar of bedside physical examination in addition to inspection, palpation, percussion, and auscultation[8]. This raises the question why we need an enhancement to physical examination in the first place and does POCUS have better diagnostic accuracy. The diagnostic performance of conventional physical examination is poor for several clinical questions that nephrologists deal with in day-to-day practice. For example, in a study including 50 patients with severely reduced left ventricular ejection fraction, the combined sensitivity of rales, edema, and elevated jugular venous pressure (JVP) was only 58% to detect an elevated pulmonary capillary wedge pressure of > 22 mmHg[9]. Similarly, in another study including 58 non-edematous patients with serum sodium less than 130 mEq/L, clinical assessment was able to accurately identify only 47% of hypovolemic and 48% of euvoletic patients[10]. Likewise, in a meta-analysis of 22 studies, pooled sensitivities of orthopnea, peripheral edema, JVP, third heart sound and rales were only 50%, 51%, 39%, 13% and 60% respectively to diagnose congestive heart failure[11]. Further, there is no conventional physical examination parameter to answer focused questions requiring visualization of internal anatomy such as the presence or absence of hydro-nephrosis, systemic venous congestion *etc.* POCUS aids in answering such questions at the bedside without having to wait for multiple consultative ultrasound studies and potentially avoiding unnecessary radiation. The diagnostic superiority of POCUS is well established in various clinical settings compared to conventional examination. For instance, in a study including 79 patients on hemodialysis, the sensitivity of lung crackles and peripheral edema was only 9% and 3% respectively to detect severe lung congestion found on lung POCUS[12]. In the context of critical illness, a study including 926 patients admitted to the intensive care unit found that 51% of those who had pulmonary edema on lung POCUS demonstrated normal auscultatory findings[13]. With respect to focused cardiac ultrasound, in a recent meta-analysis of 9 studies, the sensitivity of POCUS-assisted examination for diagnosing left ventricular dysfunction and valvular disease was found to be significantly higher compared to conventional assessment (84% *vs* 43%, and 71% *vs* 46% respectively)[14]. In addition, the utility of POCUS for rapid evaluation and management of patients with undifferentiated hypotension,

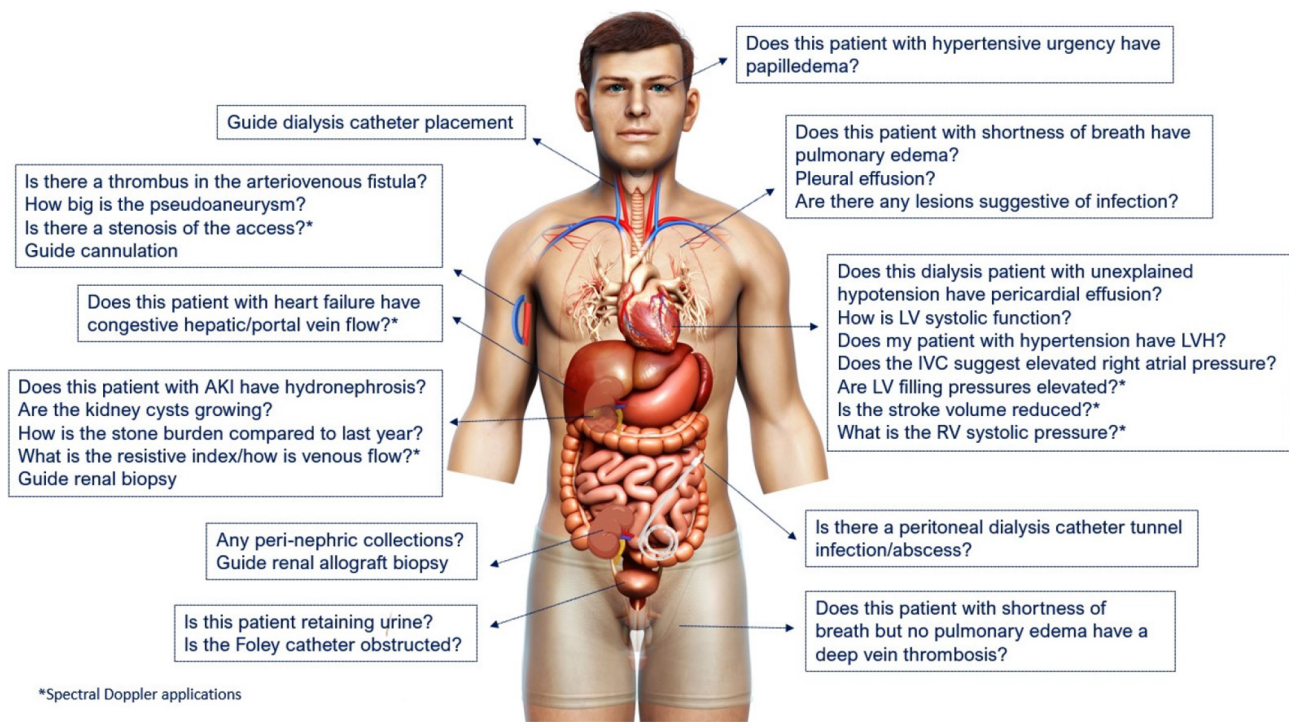


Figure 1 Scope of nephrology-related point of care ultrasonography. Organ-specific focused questions that can be answered by bedside ultrasonography. Those marked with asterisk (*) indicate advanced sonographic applications requiring a higher operator skill level/additional training. Figure reused from reference # 3 with kind permission of the American Society of Nephrology.

chest trauma and possible pericardial tamponade is well-recognized[15]. All these studies highlight the need for enhancing our bedside examination with POCUS. Furthermore, there are emerging data suggesting that POCUS enhances patient satisfaction and shared diagnostic understanding between patients and clinicians[16,17]. Even in developing countries and low-resource settings where one might expect slow adoption of technological advances due to cost issues, POCUS has shown to favorably impact clinical care. In fact, POCUS might be more beneficial in these scenarios to facilitate timely and accurate diagnosis as patients often present with advanced disease. For example, in a Tanzanian cohort of 55 hospitalized patients, a change in management plan was supported by POCUS findings in 53% cases leading to earlier initiation of appropriate treatment[18]. Similar findings were observed in a study from Sri Lanka where POCUS utilization in critically ill patients facilitated early diagnosis and/or interventions[19].

Below are a few situations commonly encountered in Onco-Nephrology practice where POCUS enhanced physical examination can provide valuable information.

CLINICAL SCENARIO 1: ACUTE KIDNEY INJURY IN CANCER

Acute kidney injury (AKI) is a frequent complication of either the underlying malignancy or its treatment and is an independent predictor of mortality in patients with cancer[20,21]. The incidence of AKI in a large Danish cohort of cancer patients was reported to be 17.5% at 1 year and 27% over the course of 5 years, which highlights the enormity of the problem[22]. Similarly, in a Chinese study, the incidence of AKI in hospitalized cancer patients was reported to be 7.5% (hospital acquired in 6% of the cases)[23]. The etiologies of AKI vary across solid organ and hematological malignancies as well as in patients undergoing stem cell transplantation. Hemodynamic AKI resulting from volume depletion is the predominant cause of AKI in patients with an underlying cancer[24] as they may develop nausea, vomiting or diarrhea as complication of cancer chemotherapy or due to the underlying cancer. Post renal obstructive etiology may be the driver of AKI in patients with genitourinary malignancies or locally invasive primary gynecological or gastrointestinal malignancies or metastatic disease[25]. Moreover, as a significant proportion of malignancies treated with radiotherapy are in the abdomen and pelvis, complications such as radiation-induced ureteral and urethral stenosis must be considered in the differential diagnosis of obstructive nephropathy in these patients[26]. Intrinsic renal injury may be mediated by nephrotoxic chemotherapy, paraproteins, glomerulopathies, contrast exposure, infiltration by the primary malignancy or progression of ischemic kidney injury[25].

POCUS considerations

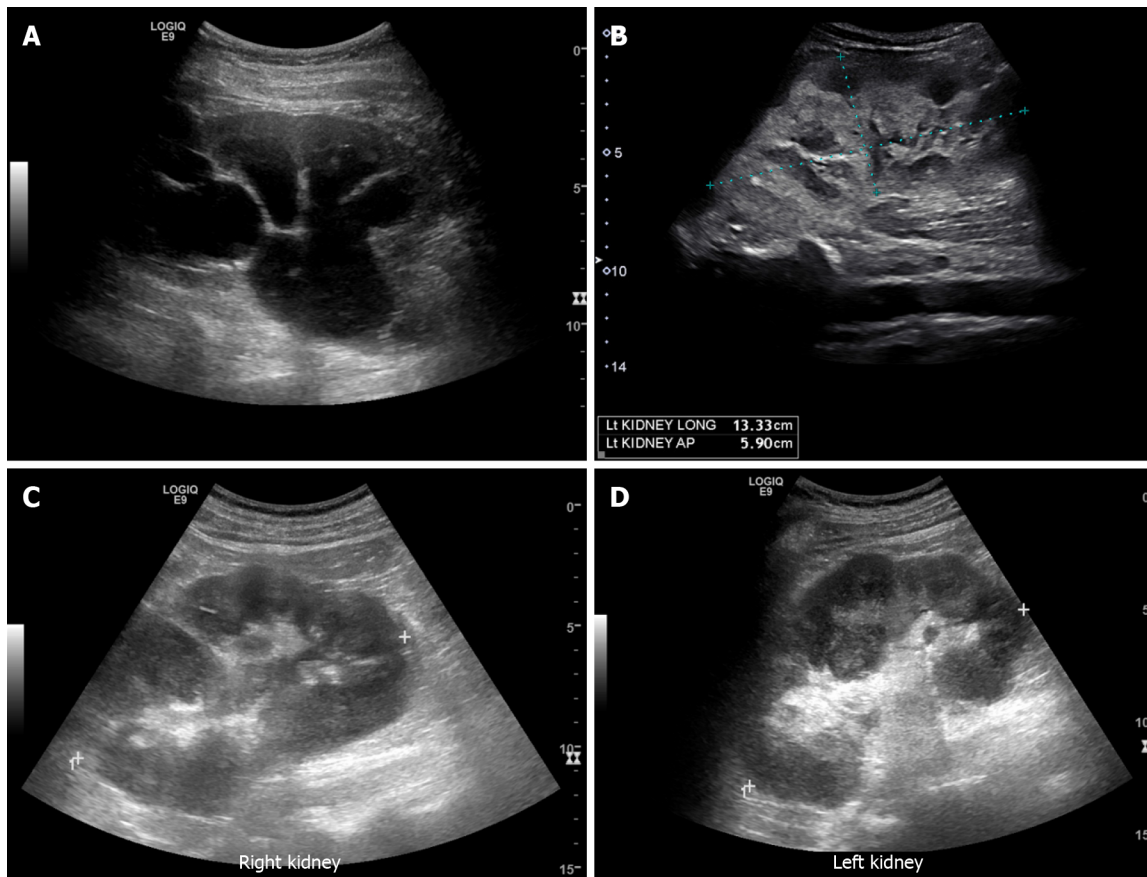
Renal sonography is frequently ordered as part of the initial diagnostic algorithm to rule out obstructive etiology, which is potentially reversible if treated promptly. Bedside POCUS can easily identify hydronephrosis and bladder masses that may be causing urinary obstruction[27]. POCUS can also help delineate intrinsic processes such as infiltrative diseases which may be arising secondary to lymphoma for instance[28]. The kidney size tends to be preserved or larger than expected in these cases with alterations noted in cortical echogenicity. Determination of kidney size and cortical echogenicity while keeping in context the clinical picture can help understand if the renal impairment appears to be a chronic vs. acute process and the realistic probability of renal recovery which can then impact the future diagnostic and therapeutic considerations for these patients[29]. We previously proposed *SECONDS checklist* for systematic interpretation of renal POCUS, which is helpful for novice users[30]. It stands for Size (renal length and thickness), Echogenicity (cortical brightness), Collecting system (obstruction), Outline (smooth *vs* irregular), Notable lesions (such as cysts and stones), Doppler (to distinguish between hydronephrosis and vasculature) and Surroundings (peri-nephric collections). **Figure 2** illustrates some of the pathologies seen on renal ultrasound in cancer patients. It is also important to evaluate urinary bladder by POCUS in any patient with AKI and/or oliguria to exclude etiologies such as obstructed Foley catheter or bladder outlet obstruction due to extrinsic compression. Moreover, automated bladder scanners cannot distinguish between pelvic ascites and urinary bladder, which may cause confusion in some cases where POCUS aids in correct diagnosis[31]. As hemodynamic AKI is the most frequent etiology of AKI in patients with cancer, the role of POCUS in this clinical scenario deserves a special mention and is discussed in more detail under volume management below.

CLINICAL SCENARIO 2: VOLUME ASSESSMENT AND MANAGEMENT

Patients with a diagnosis of cancer are often administered intravenous fluids around chemotherapy with the hope of mitigating the risk of AKI, which can lead to iatrogenic fluid overload if the volume status is not objectively assessed. Further, the volume status in these patients is often tenuous, complicated by increased losses through vomiting and diarrhea as well as third spacing due to hypoalbuminemia. Additionally, certain types of chemotherapies may cause cardiac dysfunction predisposing to volume overload. An important reason for Onco-Nephrology consultation on the inpatient Nephrology service is volume assessment and management in patients undergoing stem cell transplantation (SCT) where volume overload occurs frequently. Allogeneic SCT is a well-established treatment for various hematological malignancies as well as a few nonmalignant disorders[32]. Fluid overload in these patients significantly impacts mortality and is associated with poorer survival[33]. As such, it is imperative that we use objective bedside tools such as POCUS to assess hemodynamic status and guide therapy.

POCUS considerations

Multiorgan POCUS in these cases allows accurate volume assessment. We call this the *Pump, Pipes and Leaks* approach. The pump denotes focused cardiac ultrasound, pipes represent inferior vena cava (IVC) ultrasound and systemic venous Doppler, and the leaks indicate assessment of the extravascular lung and abdominal fluid[29] (**Figure 3**). This way, the whole hemodynamic circuit is assessed instead of relying on isolated parameters such as lung or IVC ultrasound, which are error prone. For example, B-lines on lung ultrasound (vertical artifacts signifying interlobular septal thickening) can be seen in cardiogenic pulmonary edema or an infectious process or even fibrosis. In addition to paying attention to parameters such as irregular pleural line suggestive of local pathology, assessment of left ventricular diastolic function using Doppler aids in proper diagnosis. Similarly, IVC is not reliable to assess right atrial pressure in mechanically ventilated patients. Moreover, it can be chronically dilated in patients with pulmonary hypertension and may not provide meaningful information when interpreted in isolation with respect to guiding therapy. Doppler assessment of systemic venous congestion (VExUS) aids in the management of such patients[34-36]. Detailed discussion of VExUS grading to quantify systemic venous congestion is beyond the scope of this manuscript and is concisely illustrated in **Figure 4**. On the other hand, IVC can be small despite elevated right atrial pressure in intra-abdominal hypertension. Furthermore, a small collapsible IVC can be seen both in euvoolemia and hypovolemia and cannot be used in isolation to distinguish between these two conditions. Bedside assessment of stroke volume helps in this situation as it is expected to be low in hypovolemia. Therefore, a multiparametric POCUS approach is the key to appropriate diagnosis and management of volume disorders and these findings must be interpreted in the right clinical context. As most of this information can be obtained by consultative imaging, some might question the need for clinician-performed POCUS. There are two important justifications for this: (1) Hemodynamics are dynamic. For example, a patient with a normal echocardiogram few days ago might have a completely different hemodynamic picture now. Moreover, it is not prudent to obtain a formal echocardiogram daily to monitor selected hemodynamic parameters in response to treatment when POCUS can accomplish the same during daily rounds; and (2) POCUS reduces fragmentation of care. For instance, to assess the pump, pipes and leaks, multiple consultative



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Figure 2 Renal ultrasound images demonstrating. A: Severe hydronephrosis (branching anechoic area); B: Enlarged kidney with hyperechoic cortex in a patient with myeloma; C and D: Bilateral renal involvement with lymphoma. Note irregular outline and heterogeneous parenchyma.

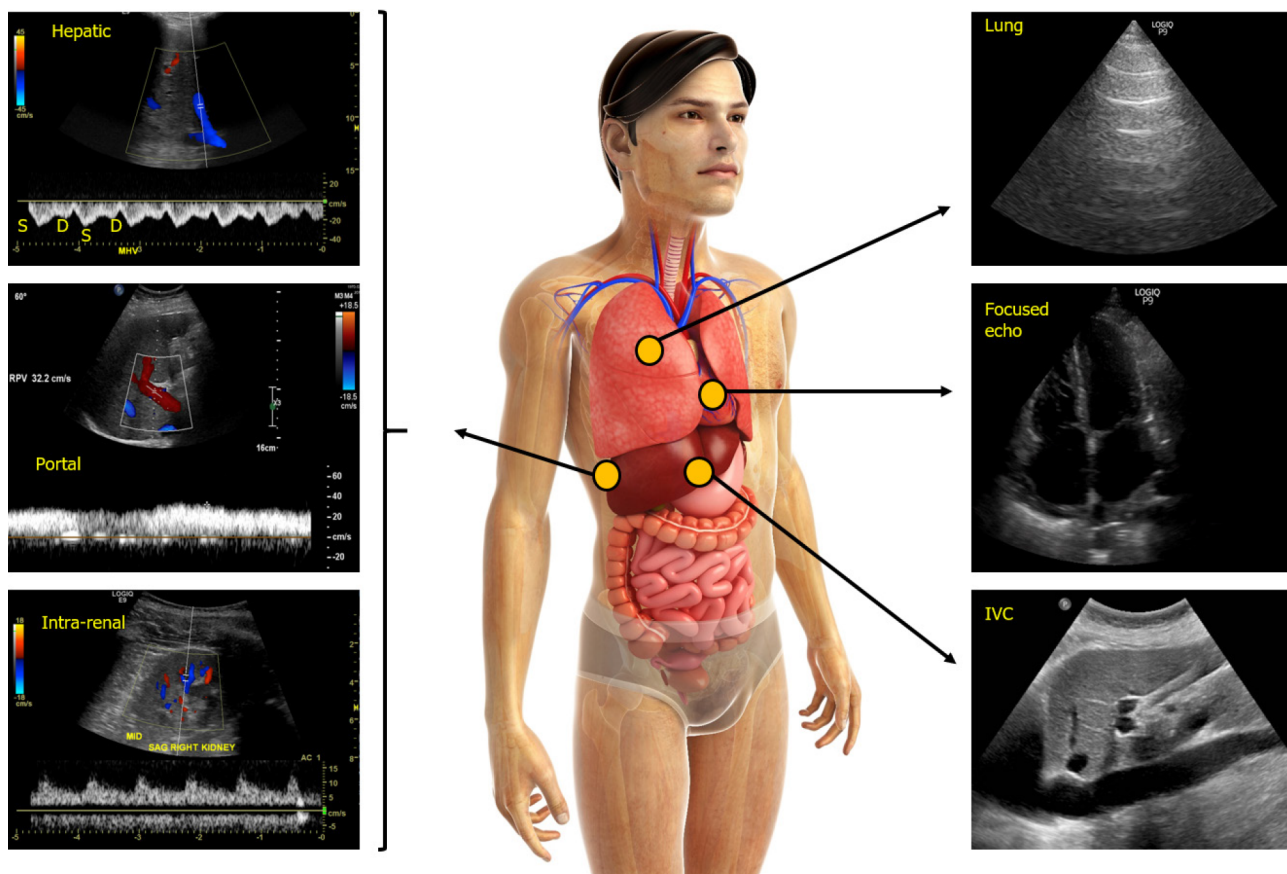
studies must be obtained – echocardiography performed by the cardiology department, a chest radiograph (lung ultrasound is typically not performed by the ultrasound department), an abdominal sonogram (to look for ascites), a right upper quadrant Doppler (for hepatic and portal vein Doppler [a part of VExUS]) and a Doppler renal ultrasound (for renal venous congestion). Conversely, a POCUS-trained physician with knowledge of the patient's clinical history/course can perform a focused assessment answering all the key questions in less than 15 min and tailor therapy accordingly.

CLINICAL SCENARIO 3: EFFUSIONS

Pleural effusion secondary to an underlying malignancy is seen in about 15% of cancers. Metastatic lung (in males) and breast cancer (in females) account for 50%-65% of all cases of malignant pleural effusion. Patients presenting with pleural effusion will require additional imaging for diagnosis and planning of therapeutic interventions. Bedside POCUS is increasingly being utilized for guidance for thoracentesis [37]. Pericardial effusions are noted in 5%-20% patients with an underlying malignancy and significantly impacts the survival and prognosis in these cases [38,39]. Pericardial involvement may result from direct extension of the tumor into the pericardial cavity or hematogenous spread. Opportunistic infections in patients undergoing cancer chemotherapy as well as deranged liver, kidney or cardiac function arising as a result of the underlying cancer or cancer chemotherapy and radiation (like anthracyclines, docetaxel, busulfan, tyrosine kinase inhibitors, arsenic trioxide which can affect the myocardium) may play a role as well in causing pericardial effusion. Majority of the pericardial effusions associated with malignancies are moderate to large in size with pericardial tamponade being noted in one third of the patients with malignant pericardial effusion with poorer outcomes reported in these patients [39]. In addition, ascites is a frequent accompaniment of gastrointestinal and metastatic malignancy.

POCUS considerations

The diagnostic superiority of POCUS to detect multiple effusions is well-established. For example, lung POCUS is more sensitive than physical examination or chest radiography for the detection of small



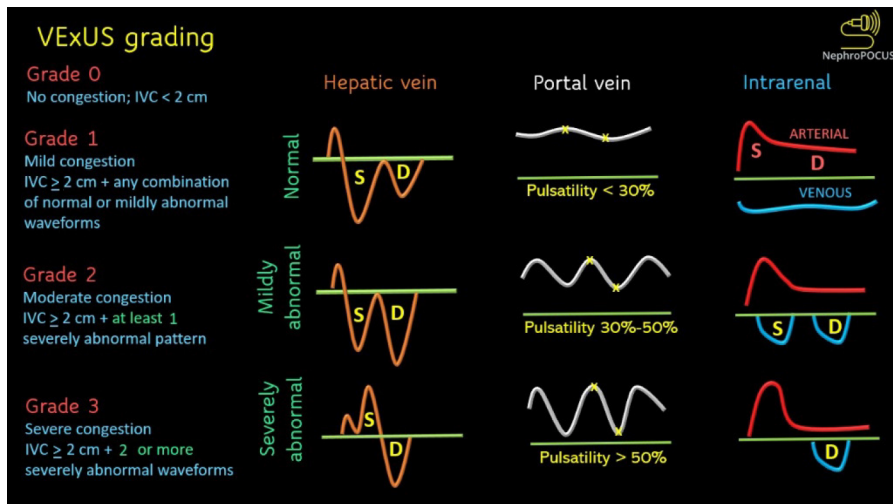
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Figure 3 Figure illustrating the integration of multi-point sonographic assessment including focused cardiac, lung and venous Doppler ultrasound. Normal waveforms are shown. IVC: Inferior vena cava. Adapted from corresponding author's prior open access publication.

pleural effusions and can detect as small as 3-5 cc of fluid in the pleural space[40-42]. In addition to visualization of pleural effusion, POCUS can help identify loculations in the fluid, thickening and nodularity of the diaphragm, findings which are relatively specific for the diagnosis of malignant pleural effusion. Ultrasound guided pleural biopsies may also be undertaken. The diagnostic accuracy of ultrasound is comparable to computed tomography (CT) in these cases while avoiding the radiation exposure associated with CT imaging. POCUS has also shown to be highly accurate for detecting pericardial effusions of any size and can detect tamponade physiology prior to that of physical examination or vital signs[43]. Therefore, POCUS-performing physician can seek timely consultations prior to clinical decompensation of the patient. Of note, the classic Beck classic triad (jugular venous distension, hypotension, and muffled heart sounds) is a late finding and is neither sensitive nor specific for tamponade[44,45]. With regard to ascites, ultrasound is substantially better than physical examination and can detect as little as 100 cc of peritoneal fluid. In an interesting study from 1982 comparing the diagnostic accuracy of physical examination with that of ultrasound for ascites, overall accuracy of physical examination maneuvers was only 58%[46]. POCUS guidance for paracentesis is essentially a standard procedure in developed countries and has shown to be associated with lower rates of bleeding, decreased hospital length of stay, and cost savings compared to the traditional landmark-based technique[47]. Recently, Nauka *et al*[48] have proposed a FASC protocol (Focused Assessment with Sonography in Cancer), a simple six-point assessment technique to assess multiple effusions in cancer patients that can be easily used by physicians with limited training. **Figure 5** illustrates the sonographic appearance of various effusions.

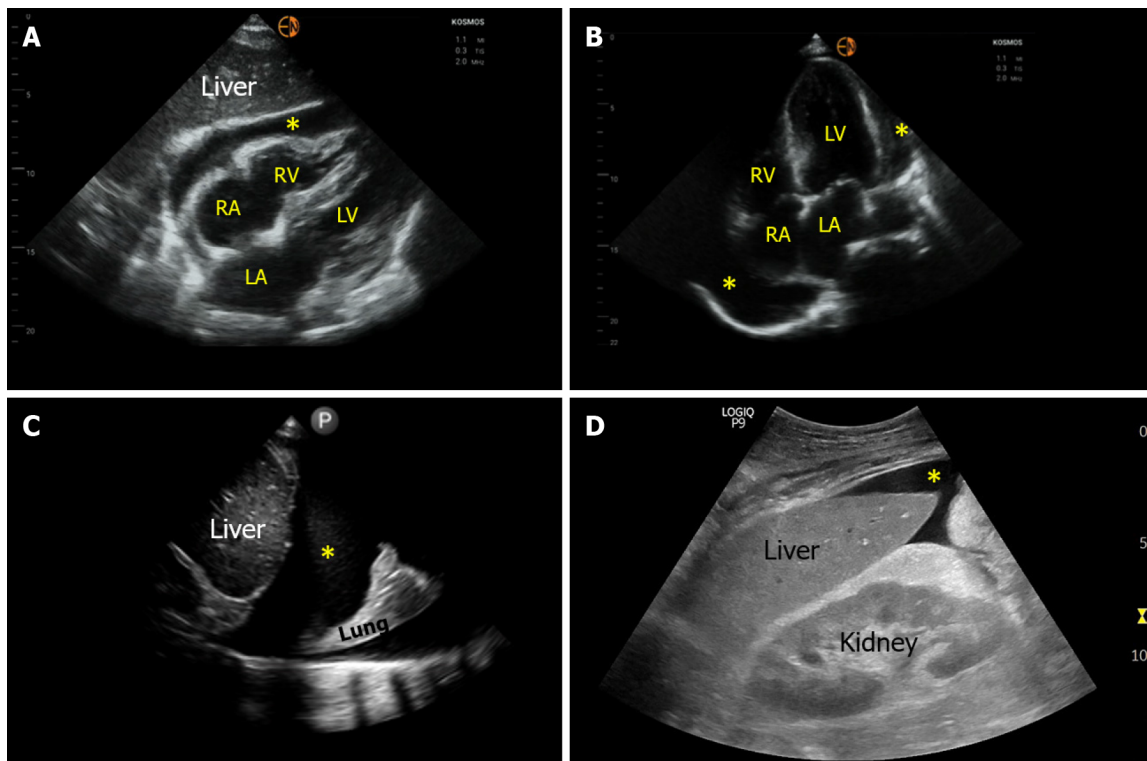
CLINICAL SCENARIO 4: HYPONATREMIA

Hyponatremia is a very common electrolyte abnormality and may be noted in up to 50% of cancer patients[49]. It negatively impacts prognosis in these patients and may be reflective of advanced underlying disease, chemotherapy toxicity and new or progressive liver or cardiac involvement[50]. Syndrome of inappropriate antidiuresis and volume depletion are the most common etiologies for hyponatremia that complicates an underlying malignancy[50,51]. The traditional diagnostic workup for



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Figure 4 Venous excess ultrasound grading. When the diameter of inferior vena cava is > 2 cm, three grades of congestion are defined based on the severity of abnormalities on hepatic, portal, and renal parenchymal venous Doppler. Hepatic vein Doppler is considered mildly abnormal when the systolic (S) wave is smaller than the diastolic (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% to 50%, and severely abnormal when it is ≥ 50%. Asterisks represent points of pulsatility measurement. Renal parenchymal vein Doppler is mildly abnormal when it is pulsatile with distinct S and D components, and severely abnormal when it is monophasic with D-only pattern. Adapted from NephroPOCUS.com with permission.



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Figure 5 Sonographic images demonstrating various effusions. A and B: Pericardial effusion (*) as seen on subxiphoid and apical 4-chamber cardiac views respectively; C: Right pleural effusion (*) seen from the lateral scanning window; D: Ascites (*) seen from the right upper quadrant. RA: Right atrium; LA: Left atrium; RV: Right ventricle; LV: Left ventricle.

hyponatremia begins with measurement of plasma and urine osmolality, urine sodium concentration and assessment of volume status[52]. Unfortunately, physical examination has been reported to have poor sensitivity and specificity in this setting, underscoring the void in our bedside assessment[10].

POCUS considerations

A bedside focused ultrasound examination using proven diagnostic parameters can provide objective assessment of volume status, which would make a case for its incorporation in the initial diagnostic algorithm of hyponatremia[53]. The Pump, Pipes and Leaks approach mentioned above works well in this setting. For example, a small collapsing IVC with low stroke volume suggests hypovolemia whereas the same IVC with normal stroke volume suggests euvoolemia. A plethoric IVC is more in favor of hypervolemia though Doppler parameters such as VExUS and transvalvular flow assessment are needed in patients with chronically dilated IVC. Several case reports have been published thus far demonstrating the utility of POCUS in the evaluation and management of hyponatremia as we furnished in our prior publication[53].

SUMMARY AND FUTURE DIRECTIONS

Current evidence clearly indicates that POCUS is superior to that of conventional physical examination in terms of diagnostic accuracy and thereby enhances physicians' confidence in clinical decision making. Future studies must aim to investigate how to better integrate this diagnostic tool in day-to-day Onco-nephrology practice to positively impact measurable outcomes. While one cannot expect mortality benefit just by incorporating a diagnostic modality, outcomes such as duration of hospitalization, time to appropriate diagnosis and treatment, effective decongestion at hospital discharge, recovery of hemodynamic AKI, improvement in patient-reported quality of life, patient and family members' understanding of the diagnosis are all important practical outcomes that POCUS can impact. On a note of caution, POCUS is operator dependent like anything else in medicine (history taking, physical examination, communication with patients) and proper training is the key to avoid unintentional patient harm. With the availability of low-cost ultraportable ultrasound equipment, POCUS is being increasingly utilized by physicians with limited or no training. It is particularly problematic when the user overestimates their skills and/or capabilities of the equipment (*e.g.*, a novice user with limited understanding of Doppler principles assesses stroke volume using suboptimal image obtained by a low-quality handheld ultrasound device resulting in false conclusions and subsequent patient mismanagement). The burden of regulating and overseeing its use falls on the individual institutions till there are uniform guidelines put forth by professional societies for POCUS training and competency assessment. As a matter of fact, Emergency Care Research Institute has listed the increased adoption of POCUS outpacing institutional safeguards as one of the top health technology hazards[54]. One cannot expect to master physical examination by attending a half- or a one-day workshop and the same applies to POCUS; longitudinal training with emphasis on image acquisition, interpretation and clinical integration is the key to achieving competency and avoiding untoward consequences. As POCUS expertise among nephrologists is sparse at this time, collaboration with experts from various POCUS-performing specialties (*e.g.*, emergency medicine, critical care) is vital for establishment of robust POCUS training programs with quality assurance measures in place.

CONCLUSION

POCUS is a valuable adjunct to physical examination in patients with cancer and renal dysfunction or fluid/electrolyte disorders. It provides better diagnostic accuracy than conventional physical examination. Proper training is the key to effectively integrate this diagnostic tool into routine clinical practice.

FOOTNOTES

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Retrospective Cohort Study

Preemptive living donor kidney transplantation: Access, fate, and review of the status in Egypt

Rabea Ahmed Gadelkareem, Amr Mostafa Abdelgawad, Ahmed Reda, Nashwa Mostafa Azoz, Mohammed Ali Zarzour, Nasreldin Mohammed, Hisham Mokhtar Hammouda, Mahmoud Khalil

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Abstract

BACKGROUND

Preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease.

AIM

To assess the rate of PLDKT among patients who accessed KT in our center and review the status of PLDKT in Egypt.

METHODS

We performed a retrospective review of the patients who accessed KT in our center from November 2015 to November 2022. In addition, the PLDKT status in Egypt was reviewed relative to the literature.

RESULTS

Of the 304 patients who accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were 31.7 ± 13 years and 12.8 ± 3.5 mL/min/1.73 m², respectively. Fifty-nine patients had KT, including 3 PLDKTs only (5.1% of total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (39.3%). In multivariate analysis, known primary kidney disease ($P = 0.002$), patient age ($P = 0.031$) and sex ($P = 0.001$) were independent predictors of achievement of KT in our center. However, PAKT was not significantly ($P = 0.065$) associated with the achievement of KT. Review of the literature revealed

lower rates of PLDKT in Egypt than those in the literature.

CONCLUSION

Patient age, sex, and primary kidney disease are independent predictors of achieving living donor KT. Despite its non-significant effect, PAKT may enhance the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

Key Words: Access to kidney transplantation; Donor regression; Kidney transplantation; Living donors; Preemptive kidney transplantation; Transplantation

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Core Tip: Patients with preemptive access to kidney transplantation (PAKT) may have significant differences from those with conventional access to KT, warranting more evaluation. In this study, known primary kidney disease was an independent factor of achievement of living donor KT (LDKT). In addition, the older age and female sex were independent predictors of non-achievement of LDKT. However, unavailability, regression, and exclusion of LDs and patient regression on starting dialysis may prevent achievement of preemptive LDKT (PLDKT) in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable or variably better outcomes than the conventional LDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, the rate of PLDKT is still lower than that of other countries, warranting implementation of effective strategies to promote PLDKT.

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INTRODUCTION

Preemptive kidney transplantation (PKT) is defined as receiving kidney transplantation (KT) before initiation of maintenance dialysis in patients with end-stage renal disease (ESRD)[1,2]. This definition may vary from one KT program to another, where patients who receive dialysis sessions sporadically or as conditioning pre-transplantation sessions for no more than 1 wk may be included in this definition[2-6]. The evolution of PKT was more than 30 years ago[7], when it passed through an insidious course and gained variably insufficient interests among the physicians and surgeons in the KT community[1,5]. Many initiatives and programs have been triggered to promote PKT, especially in the sector of living donor kidney transplantation (LDKT). These initiatives promote living kidney donation (LKD) programs as the most effective contributor to PKT[4-7]. PKT is a time-based KT strategy controlled by setting the timing of KT surgery at a point just before the start of regular dialysis as much as possible. This philosophy represents the natural course of management of most diseases. However, it has generated debate along the different axes of KT, such as the proposed lead-time bias effect on the outcomes of PKT[8]. The incidence of PKT has improved gradually from 2% in its early years to 6%-7% in the last years. Most cases come from LDKT programs, where it may reach up to 34% in some countries that adopt LDKT programs[6,9]. The latter percentage refers to the fundamental role of LD in the promotion of PKT strategy[10]. Preemptive access to KT (PAKT) and waitlisting are other effective contributors to PKT. Hence, they are fundamental issues in PKT literature[1,11]. However, they have mostly been ignored in research from Egypt, where only LDKT is performed in adults[9,12-14] and pediatrics[15-17].

We assessed the percentage of patients with PAKT and their fate regarding the receipt of preemptive LDKT (PLDKT).

MATERIALS AND METHODS

Study design

A retrospective review was performed for the electronic and manual records of patients with ESRD who sought LDKT in our center from November 2015 to November 2022. The study included both patients with PAKT, which was defined as the presentation of a patient with chronic kidney disease (CKD) stage 4 or 5 for KT prior to the start of regular dialysis and those with conventional access to KT (CAKT). The exclusion criterion was patients who refused KT before starting the preparation for LDKT (Figure 1). The relevant demographic characteristics of the patients and potential donors including age, sex, and relatedness to the potential donors were reviewed. Also, the clinical data including the primary kidney disease, estimated glomerular filtration rate (eGFR) at presentation, outcomes of preparation to KT, causes of deferring LDKT, and fate of the patients and donors were studied. We used the CKD-Epidemiology Collaboration creatinine equation to estimate eGFR for patients with PAKT[18].

Also, a review of the literature was performed to assess PLDKT in KT studies from Egypt. The KT center volume, pre-KT characteristics, and percentages and outcomes of PLDKT were reviewed. Furthermore, the literature was reviewed for the incidence of PLDKT in studies from other countries and large-volume KT registries.

This study was conducted as a topic in a KT research project regarding the outcomes of LDKT at our center. The institutional review board number is 17200148/2017.

Statistical analysis

Statistical analyses were performed with EasyMedStat (version 3.21.4; www.easymedstat.com). Continuous variables are presented as the mean $\pm$ standard deviation and range. However, categorical variables are presented as the number and percentage of each category. We created two groups (PAKT and CAKT) according to the status of dialysis at the time of access to transplantation. Normality and heteroskedasticity of continuous data were assessed with the White test (or with Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with the unpaired Student *t*-test, Welch *t*-test, or Mann-Whitney *U* test according to the data distribution. Categorical outcomes were compared with the chi-squared or Fisher's exact test accordingly. Multivariate logistic regression was performed to assess the factors contributing to achievement of KT in our center. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. $P < 0.05$ was considered statistically significant.

RESULTS

Between November 2015 and November 2022, 325 patients attended our center for KT. Twenty-one (6.5%) patients changed their mind or were not serious in accessing KT. The remaining 304 patients were differentiated into PAKT and CAKT groups (Figure 1). The former group included 32 patients (10.5%) who were not on dialysis at the time of access to KT and the latter group included 272 (89.5%) patients with a mean (range) duration of hemodialysis of 6.3 ± 10.5 (0.5–108) mo. Both groups were compared for their demographic and clinical characteristics (Table 1). Follow-up after regression or exclusion decision varied from 3 mo to 6 years.

In the PAKT group, 29 patients (90.6%) failed to receive PLDKT due to original donor unavailability (25%), exclusion (28.6%), regression (3.6%), financial causes (3.6%), and patients' regression from KT when starting regular dialysis (39.3%) (Table 1). Hence, PLDKT was carried out in 3 patients only, representing 5.1% of the total KTs and 9.4% of patients with PAKT. One of these three patients died from complications of the coronavirus disease 2019, 6 mo after KT. The other 2 patients were still living with a functioning graft for 68 and 12 mo at the time of writing of this article. The detailed characteristics of patients with PAKT are presented as individual patients (Table 2). The mean (range) age was 31.7 ± 13 (13–60) years. Most of the patients presented with stage 5 CKD. The mean (range) for serum creatinine level and eGFR was 6 ± 1.6 (3.2–9.8) mg/dL and 12.8 ± 4.8 (7–28) mL/min/1.73 m², respectively.

In the current cohort of patients, the total number of patients who had been transplanted at our center (59 patients) or at other centers (29 patients) was 88 (28.9%) patients. In a comparison between the patients who achieved (59 patients) and those who failed to achieve (245 patients) LDKT in our center, there were significant differences in age ($P = 0.034$), sex ($P < 0.001$), primary kidney disease ($P = 0.008$), number of potential donors ($P = 0.003$), and acceptance/exclusion rate of evaluated donors ($P < 0.001$) per patient (Table 3).

In multivariate analysis, known primary kidney disease ($P = 0.002$) was associated with higher rates of achievement of KT in our center. In addition, female sex ($P = 0.001$) and older patients ($P = 0.031$) were significantly associated with lower rates of achievement of KT in our center. However, PAKT ($P = 0.065$) and multiple potential donors ($P = 0.529$) were not significantly associated with the rate of achievement of KT in our center (Table 4).

Table 1 A comparison of the demographic and clinical characteristics of the patients with preemptive access to kidney transplantation and those with conventional access to kidney transplantation, *n* (%)

Variables	PAKT, <i>n</i> = 32	CAKT, <i>n</i> = 272	<i>P</i> value
Age in yr, mean $\pm$ SD (range)	31.7 $\pm$ 13 (13-60)	32.1 $\pm$ 11.5 (12-66)	0.677
Sex			
Men	22 (68.8)	213 (78.3)	0.263
Women	10 (31.2)	59 (21.7)	
Primary kidney disease			
Glomerulonephritis	3 (9.4)	8 (2.9)	< 0.001
Hereditary disease	3 (9.4)	6 (2.2)	
Obstructive uropathy	4 (12.5)	8 (2.9)	
Systemic disease	4 (12.5)	14 (5.2)	
Urolithiasis	3 (9.4)	7 (2.6)	
Unknown	15 (46.9)	229 (84.2)	
Number of potential donors ¹			
Patients presented without donors	8 (25)	36 (13.2)	0.088
With one donor	17 (53.1)	187 (68.8)	
With two donors	4 (12.5)	40 (14.7)	
With three donors	3 (9.4)	9 (3.3)	
Donor evaluation	24	236	
Patients with evaluated donors	20	194	
With accepted donor(s)	10 (50)	89 (45.9)	0.232
With one donor excluded	7 (35)	75 (38.7)	
With two donors excluded	0 (0)	15 (7.7)	
With three donors excluded	1 (5)	2 (1)	
With excluded and accepted donors	2 (10)	13 (6.7)	
Number of not evaluated donors per patient	6	56	
One donor	3 (50)	51 (91.1)	0.024
Two donors	3 (50)	4 (7.1)	
Three donors	0 (0)	1 (1.8)	
Order of the accepted donor	12	102	
First	10 (83.3)	87 (85.3)	0.634
Second	1 (8.3)	11 (10.8)	
Third	1 (8.3)	4 (3.9)	
Accepted donor age (yr), mean $\pm$ SD (range)	38.1 $\pm$ 9 (25-53)	40.6 $\pm$ 10.4 (21-60)	0.39
Patient-donor relatedness degree			
First	5 (41.7)	55 (53.9)	0.234
Second	5 (41.7)	40 (39.2)	
Third	1 (8.3)	6 (5.9)	
Unrelated	1 (8.3)	1 (1)	
Sex of accepted donors			
Women	7 (58.3)	66 (64.7)	0.754
Men	5 (41.7)	36 (35.3)	

Accepted donor commitment			
Donated	4 (33.3)	55 (53.9)	0.171
Regressed	1 (8.3)	16 (15.7)	
Released	7 (58.3)	31 (30.4)	
Number of excluded donors per patient			
One donor	7 (77.8)	84 (80)	0.262
Two donors	1 (11.1)	19 (18.1)	
Three donors	1 (11.1)	2 (1.9)	
Main causes of donor exclusion			
Medical causes	1 (10)	51 (51.5)	0.027
Immunologic mismatch	7 (70)	34 (34.3)	
Combined medical and immunologic	2 (20)	14 (14.1)	
Main causes of donor release			
Financial causes	0 (0)	3 (10.7)	0.235
Patient death	0 (0)	3 (10.7)	
Patient non-candidacy	0 (0)	10 (35.7)	
Patient regression	5 (100)	12 (42.9)	
Achievement of kidney transplantation			
Failed	25 (78.1)	191 (70.2)	0.568
Transplanted in our center	4 (12.5)	55 (20.2)	
Transplanted in another center	3 (9.4)	26 (9.6)	
Cause of non-achievement of transplantation in our center			
Donor exclusion	8 (28.6)	88 (40.6)	0.035
Donor regression	1 (3.6)	16 (7.4)	
Donor unavailability	7 (25)	37 (17.1)	
Financial causes	1 (3.6)	13 (5.6)	
Patient non-candidacy	0 (0)	25 (11.5)	
Patient death	0 (0)	5 (2.6)	
Patient regression	11 (39.3)	33 (15.2)	
Fate of recipients who failed to have transplantation in our center			
Death	0 (0)	13 (6)	0.213
On hemodialysis	24 (85.7)	147 (67.7)	
Transplantation in another center	3 (10.7)	26 (12)	
Unknown	1 (3.6)	31 (14.3)	

¹The headings of the donor evaluation and non-evaluation may include overlapping numbers due to different outcomes of the evaluation of multiple donors, resulting in non-complementary values relative to the total number of patients in both groups.

CAKT: Conventional access to kidney transplantation; PAKT: Preemptive access to kidney transplantation; SD: Standard deviation.

Review of the literature for PLDKT in studies from Egypt revealed that only eight articles addressed PLDKT (Table 5). These articles were from three academic centers only, including seven original research and one opinion article. The percentage of PLDKT varied between 6.4% in adults and 23% in pediatrics. No articles addressed the PAKT or waitlisting. The reported patient and graft survival rates were similar to those of conventional LDKT (CLDKT) in the literature.

In addition, a review of the English literature for the incidence of PLDKT in other countries revealed higher rates than those from Egypt. However, they reported on PKT from both LDs and deceased donors. There were higher rates of PKT in patients who received LDKT than in those who received deceased donor KT (Table 6). In 1987, Migliori *et al* [19] were the first to evaluate the effects and

Table 2 Detailed characteristics and fate of patients with preemptive access to kidney transplantation, *n* = 32

Case Number	Age in yr	Sex	No. of Potential donors relatedness	Primary kidney disease	Serum creatinine in mg/dL	Stage of CKD, eGFR as mL/min/1.73 m ²	PLDKT receipt	Cause of cancelled PLDKT	Fate of the patient
Case 1	48	Male	3 (Wife, Sister, daughter)	Unknown	8.5	5 (7)	None	Donor exclusion	On HD for 20 m then CLDKT in our center
Case 2	25	Male	1 (Mother)	CMU	5.5	5 (14)	None	Donor exclusion	On HD for 62 m
Case 3	28	Male	3 (Brothers)	Unknown	8.2	5 (8)	None	Patient regression	On HD for 74 m
Case 4	59	Female	2 (Sons)	Diabetic nephropathy	5.4	5 (11)	None	Patient regression	On HD 75 m
Case 5	47	Male	2 (Unrelated)	ADPCKD	4.8	5 (14)	Yes	NA	Living with a functioning graft for 68 m
Case 6	26	Male	1 (Brother)	Urolithiasis	7.8	5 (9)	None	Patient regression	On HD then lost to follow up
Case 7	27	Male	1 (Aunt)	Unknown	6.9	5 (10)	None	Patient regression	On HD then CLDKT in another center
Case 8	38	Male	1 (Unrelated)	ADPCKD	7.4	5 (9)	None	Donor exclusion	On HD for 34 m
Case 9	22	Female	None	Unknown	4.8	5 (12)	None	Donor unavailability	On HD for 33 m
Case 10	19	Female	None	Unknown	3.5	4 (19)	None	Donor unavailability	On HD for 24 m
Case 11	24	Male	None	GN	4.4	4 (18)	None	Donor unavailability	On HD then lost to follow-up
Case 12	13	Male	1 (Mother)	Congenital VURD	4.6	4 (18)	Yes	NA	Died from COVID-19 complications
Case 13	14	Male	1 (Mother)	PUV	5.3	4 (16)	None	Donor exclusion	On HD then CLDKT in another center
Case 14	23	Male	1 (Mother)	Urolithiasis	5.1	5 (15)	None	Patient regression	On HD for 18 m
Case 15	34	Female	1 (Sister)	Unknown	8.6	5 (8)	None	Donor regression	On HD for 6 m before death
Case 16	52	Male	1 (Brother)	ADPCKD	6.2	5 (10)	None	Donor exclusion	On HD for 28 m
Case 17	19	Male	None	VURD	3.2	4 (28)	None	Donor unavailability	On HD 24 m
Case 18	36	Male	1 (Sister)	Hypertensive nephropathy	6.8	5 (10)	None	Patient regression	On HD for 26 m
Case 19	34	Male	3 (Unrelated)	ADPCKD	7.5	5 (9)	None	Donor exclusion	On HD for 27 m
Case 20	34	Male	2 (Brother, Sister)	Diabetic nephropathy	8.4	5 (8)	None	Patient regression	On HD for 28 m
Case 21	15	Male	1 (Mother)	Unknown	5.4	5 (15)	None	Donor exclusion	On HD for 6 m then lost to follow-up
Case 22	44	Male	1 (Brother)	Urolithiasis	6.7	5 (10)	None	Patient regression	On HD for 8 m then lost to follow-up
Case 23	40	Female	1 (Cousin)	Unknown	6.7	5 (7)	None	Donor regression	Unknown
Case 24	44	Male	1 (Brother)	Hyperuricemia	5.6	5 (12)	None	Donor exclusion	On HD for 13 m
Case 25	19	Male	1 (Mother)	Congenital	4.7	4 (17)	Yes	NA	Living with a

VURD									functioning graft for 12 m
Case 26	23	Female	1 (Mother)	Unknown	6.3	5 (12)	None	Patient regression	On HD for 18 m
Case 27	60	Male	None	Unknown	5.6	5 (11)	None	Donor unavailability	On HD then CLDKT in another center
Case 28	29	Male	1 (Sister)	GN	3.9	4 (19)	None	Donor exclusion	On HD 8 m
Case 29	25	Female	1 (Brother)	Unknown	9.8	5 (7)	None	Patient regression	On HD for 6 m
Case 30	47	Female	None	Unknown	6.4	5 (12)	None	Patient regression	On HD for 16 m
Case 31	25	Male	None	FSGS	4.5	4 (18)	None	Donor unavailability	On HD for 5 m
Case 32	21	Female	None	Unknown	4.2	4 (18)	None	Donor unavailability	On HD for 3 m

ADPCKD: Autosomal dominant polycystic kidney disease; CKD: Chronic kidney disease; CLDKT: Conventional living donor kidney transplantation; CMU: Congenital megaureter; COVID-19: Coronavirus disease 2019; eGFR: Estimated glomerular filtration rate; FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; HD: Hemodialysis; N/A: Not applicable; PLDKT: Preemptive living donor kidney transplantation; PUV: Posterior urethral valve; VURD: Vesicoureteral reflux disease.

outcomes of PKT in a large study from the United States, reporting a PKT rate of 7.6%. They were followed by two European studies with variable rates[20,21]. Then, five studies presented data from registries from United States and Canada and reported higher PKT rates up to 21% of the total KT and more than 29% of LDKTs[22-26]. In addition, three studies from Japan, Australia, and Korea presented PLDKT rates up to 22% in patients receiving LDKT[27-29]. In 2009, two studies of mixed LD and deceased donor KT showed higher rates of PLDKT about 39%[30,31]. Between 2011 and 2016, five studies of pediatric and adult KT showed similar rates[2,32-35]. In the last 3 years, many studies have reported high PLDKT rates more than 34% of LDKTs[36-38].

DISCUSSION

We addressed the topic of PKT in Egypt, because there is a question that whether the reported incidence of PLDKT correlates with the international values. Because this question may entail addressing the barriers and the promoting strategies of PLDKT, we performed this retrospective study to assess the outcomes of patients accessed KT at our center. In addition, review of PLDKT publications coming from Egypt was carried out in the context of the international literature, either as specific studies for PLDKT within LDKT cohorts or as combined LDKT and deceased donor KT researches. There is significant variability in the rates of PKT all over the world. In most studies, the proportions of PLDKT are higher than those of PKT in deceased donor KT. Most of these studies showed significantly higher incidences in adults and pediatrics. However, because the total percentages of LDKT are lower than those of KT from deceased donors, the frequency of PKT from deceased donors represented the majority of cases of PKT in some studies. However, relative to the total numbers of donor source, the percentages of PLDKT of total LDKTs are steadily higher than those of PKT from the total deceased donor KTs (Table 6).

In Egypt, there is an obvious lack of research on PKT represented by the small number of studies that was found in this topic[12-16]. These studies were mostly retrospective and presented as few centers' experiences or small cohorts of patients. Hence, the volume of research on PLDKT is relatively small, referring to that PKT does not seem to be in the focus of research. PLDKT has just been mentioned as a category within the total cohorts of KT from centers with well-established KT programs[13,17]. On the other hand, a few studies were specifically conducted to study PLDKT outcomes in comparison to CLDKT[9,12]. This may be a part of the lack in the international literature, which has a slowly propagating body of research on PKT[33,38]. Currently, the literature refers to some sort of practical negligence of PKT in many forms, including disparities in access to PKT among the waitlisted patients. In a study from the United States, relative to the rates of White (38%) and Black (31%) patients on the waiting list, there was a significant difference between the rates of White (65%) and Black (17%) patients who had PKT in 2019[1]. Also, there is a substantially lower rates of PAKT among certain demographic groups that may face challenges in engaging with complex health care systems. Patients with low levels of education and those with physician-dependent choice of KT are other groups with disparities in the access to PKT. Inequities in access to KT require substantial efforts and multiple remedies[1]. Unfortunately, there is no studies have been conducted in Egypt to measure the rates of access to PLDKT so far.

Table 3 A comparison of the variables affecting the achievement ($n = 59$) and non-achievement ($n = 245$) of kidney transplantation in our center, n (%)

Variables	Achievement, $n = 59$	Non-achievement, $n = 245$	<i>P</i> value
Age in yr, mean $\pm$ SD (range)	29 $\pm$ 9.9 (13-57)	32.8 $\pm$ 11.9 (12-66)	0.034
Sex			
Male	56 (94.9)	179 (73.1)	< 0.001
Female	3 (5.1)	66 (26.9)	
Dialysis status			
Preemptive access	4 (6.8)	28 (11.4)	0.354
On regular dialysis	55 (93.2)	217 (88.6)	
Primary kidney disease			
Unknown causes	41 (69.5)	202 (82.4)	0.008
Systemic diseases	3 (5.1)	18 (7.4)	
Renal diseases	15 (25.4)	25 (10.2)	
Number of potential donors per patient ¹			
Donor unavailability	0 (0)	44 (18)	0.003
One donor	43 (72.9)	161 (65.7)	
Two donors	13 (22)	31 (12.6)	
Three donors	3 (5.1)	9 (3.7)	
Outcome of donor evaluation ¹			
Accepted	48 (81.4)	51 (32.9)	< 0.001
Excluded	0 (0)	100 (64.5)	
Excluded and accepted	11 (18.6)	4 (2.6)	
Number of not-evaluated donors per patient ¹			
One donor	4 (100)	51 (86.4)	> 0.999
Two donors	0 (0)	7 (11.9)	
Three donors	0 (0)	1 (1.7)	
Chronological order of accepted donor ¹	$n = 59$	$n = 55$	
First	48 (81.4)	49 (89.1)	0.596
Second	8 (13.6)	4 (7.3)	
Third	3 (5.1)	2 (3.6)	
Age of accepted donors, mean $\pm$ SD (range)	40.2 $\pm$ 10.9 (21-60)	40.5 $\pm$ 9.5 (26-58)	0.937
Degree of relatedness of accepted donors ¹			
First	34 (57.6)	26 (47.3)	0.339
Second	20 (33.9)	25 (45.4)	
Third	3 (5.1)	4 (7.3)	
Unrelated	2 (3.4)	0 (0)	
Sex of accepted donor ¹			
Male	20 (33.9)	21 (38.2)	0.779
Female	39 (66.1)	34 (61.8)	
Number of excluded donors per patient ¹	$n = 11$	$n = 102$	
One donor	8 (72.7)	82 (80.4)	0.572
Two donors	3 (27.3)	17 (16.7)	

Three donors	0 (0)	3 (2.9)	
Main causes of donor exclusion ¹	<i>n</i> = 9	<i>n</i> = 100	
Medical causes	5 (55.6)	47 (47)	0.462
Immunologic mismatches	2 (22.2)	39 (39)	
Combined medical and immunologic causes	2 (22.2)	14 (14)	

¹The values and percentages of the donors are not complementary to the total number of patients, because there were multiple donors for 56 patients who had overlapping outcomes of evaluation and fate.

SD: Standard deviation.

Table 4 Multivariate logistic regression analysis of the variables influencing the achievement of kidney transplantation in our center

Variables	Modality	Odds ratio	P value
Age	Younger <i>vs</i> older	0.97 (0.94-0.997)	0.031
Sex	Men <i>vs</i> women	0.14 (0.04-0.46)	0.001
Dialysis status	Preemptive <i>vs</i> on dialysis	0.31 (0.09-1.1)	0.065
Primary kidney disease	Known <i>vs</i> unknown	3.24 (1.5-6.9)	0.002
Number of potential donors	One <i>vs</i> multiple	0.81 (0.42-1.57)	0.529

The current study showed that PAKT represented only 10.5% of patients who were referred to KT in our center.

From the reviewed literature, the reported incidence of PLDKT in the different Egyptian KT centers was relatively lower than the international values (Tables 5 and 6). The range was 5%-6% of the total KTs that were performed in these centers[12,13]. However, the incidence was higher, when PLDKT was studied in a certain category of population, such as pediatrics with low-body weight[16,17]. Similarly, the rate of PLDKT was 5.1% in the current study. However, these values are still significantly lower than the values reported in the international literature (Table 6).

Patients with PAKT may have high education levels, payment resources, married status, residence near to KT centers, and younger age than those with CAKT. Unknown primary diseases and glomerulonephritis seemed to be the most common categories of primary kidney disease in adults[9,12,21]. Among pediatrics, reflux nephropathies, nephrotic syndromes, and congenital anomalies are the commonest primary diseases[15,16]. In addition, PLDKT patients had a lower likelihood of testing positive for hepatic viruses and receiving a blood transfusion than the CLDKT patients[12]. Of the 304 patients who accessed LDKT in our center, only 32 patients had PAKT. In turn, only 3 patients succeeded in having PLDKT and they included 2 children and 1 adult patient. They had congenital or hereditary diseases as primary causes of ESRD and the donors were unrelated donor in one case and mothers in the other 2 cases.

A large retrospective study from Mansoura Urology and Nephrology Center studied the course and outcomes of PLDKT and reported an incidence of 6.4%. In addition, it showed that there was only a significant difference in the percentages of patients who died with functioning grafts due to cardiovascular disorders and respiratory infections. The former cause was higher in PLDKT, while the latter was higher in CLDKT[12]. In a smaller prospective comparative study, we found that the incidence of acute graft rejection was significantly higher among early LDKT (ELDKT) patients than in PLDKT patients. However, the incidence of lymphoceles was significantly higher in PLDKT patients than in patients receiving ELDKT[9]. In the current study, the rates of non-candidacy and death during preparation to KT were lower in patients with PAKT (0%) than in patients with CAKT (10.7% and 35.7%, respectively). These rates may be because patients in the former group were healthier than those in the latter group.

The previous characteristic may be a surrogate of the concerns raised about the proposed effect of the lead-time bias on the advantaged outcomes of PLDKT. However, there may be a different perspective, regarding this postulation. We hypothesized that the proposed effects are a mere component of the strategy of PKT. This could simply be explained by considering the PKT and non-PKT as consecutive rather than parallel processes along the course of ESRD. PKT is an early step in the management of ESRD. So, the time factor should be considered a promotor rather than a confounder to PKT process. On the other hand, the idea of removal of the lead-time bias means discarding the spirit of the entire process of PKT[8]. The best support of this perspective is studying the outcomes of KT relative to the time-point at which KT is performed. Goldfarb-Rumyantzev *et al*[39] designed a study based on this idea and it revealed significant survival advantages when KT was performed before 180 d of dialysis.

Table 5 Preemptive living donor kidney transplantation in publications from Egypt

Ref.	Publishing place	Settings	Type	Aim	Scope relative to PLDKT	Target age group	Outcomes relative to ELDKT/ CLDKT	Number of patients; PLDKT/Total (Percentage of PLDKT)
El-Agroudy <i>et al</i> [12]	<i>Transplantation</i>	Mansoura University	Retrospective comparative	Compare outcomes of CLDKT & PLDKT	Specific	Mixed	Comparable, except in death with functioning graft was due to CVD in PLDKT <i>vs</i> respiratory infections in CLDKT	82/1279 (6.4%)
Bakr and Ghoneim[14]	<i>Saudi J Kidney Dis Transpl</i>	Mansoura University	Retrospective series	Present experience in KT	General	Mixed	Overall graft survival rates were 76% and 52% at five and 10-yr, respectively	82/1690 (4.9%)
El-Husseini <i>et al</i> [15]	<i>Pediatr Nephrol</i>	Mansoura University	Retrospective series	Evaluate outcomes of pediatric LDKT	General	Pediatrics	5-yr graft survival was 73.6%	51/216 (23%)
Mosaad <i>et al</i> [16]	<i>Dial Transpl</i>	Mansoura University	Retrospective series	Study LDKT survival in low-weight children	General	Pediatrics	PLDKT might provide better graft survival	9/63 (14.3%)
Saadi <i>et al</i> [13]	<i>Egyptian J Int Med</i>	Cairo University	Retrospective series	Identify KT Epidemiology in Cairo University hospitals	General	Mixed	Most of patients and donors were males, mostly as LDKT	14/282 (5%)
¹ Gadelkareem <i>et al</i> [9]	<i>Afr J Urol</i>	Assiut University	Prospective comparative	Compare short term outcomes of ELDKT & PLDKT	Specific	Adults	Comparable, except AR higher in ELDKT; Lymphocele incidence was higher in PLDKT	PLDKT 30/45; ELDKT 15/45
Gadelkareem <i>et al</i> [8]	<i>Exp Tech Urol Nephrol</i>	Assiut University	Opinion	Suppose that lead time should not be a bias effect in PKT	Specific	Mixed	Lead time is a mere character of PKT rather than a bias	NA
Fadel <i>et al</i> [17]	<i>Pediatr Transpl</i>	Cairo University	Retrospective series	Present experience in pediatric KT	General	Pediatrics	Timely referral and parent education were recommended	PLDKT 11/148 (7%); ELDKT 59/148 (40%)
Index study	<i>World J Nephrol</i>	Assiut University	Retrospective series	Present experience	Specific	Mixed	Urological causes are main contributor	PLDKT 3/59 (5.1%)

¹Early living donor kidney transplantation was defined as receiving kidney transplantation within 6 mo from starting regular dialysis.

AR: Acute rejection; CLDKT: Conventional living donor kidney transplantation; CVD: Cardiovascular disease; ELDKT: Early living donor kidney transplantation; KT: Kidney transplantation; LDKT: Living donor kidney transplantation; N/A: Not applicable; PKT: Preemptive kidney transplantation; PLDKT: Preemptive living donor kidney transplantation.

Internationally, many articles have addressed the barriers of PKT. The unavailability of a suitable, willing donor is a major confounder to PLDKT[40-42]. In accordance, the current results revealed that younger age, male sex, and known primary kidney disease of patients accessing KT in our center were independent predictors of achievement of KT after preparation. However, the dialysis status (PAKT *vs* CAKT), number of potential donors, and their acceptance/exclusion rates were not significantly associated with the achievement of KT. The non-significant effect of PAKT may be attributed to the delayed access of the patients with ESRD. Most of our patients with PAKT were in stage 5 CKD and a mean eGFR of 12.8 ± 4.8 mL/min/1.73 m², when they first presented to our clinic. This value of eGFR is comparable to the reported values that allow successful PLDKT[33,43], but these patients were not prepared or waitlisted before presentation to the KT unit. Hence, they needed long duration for preparation, which might be, with donor exclusion, the causes of missing the chance of PLDKT. In addition, the delayed access might be attributed to absence of a well-configured waitlisting programs in our country to refer and prepare patients at the suitable stages of ESRD. On the other hand, there are many underlying primary renal diseases that may predispose to a very late presentation of a significant proportion of patients, such as the status of pending dialysis at first discovery of their ESRD[44].

Problems of unavailability of a well-integrated healthcare system that facilitates early detection of CKD patients and timely referral to KT centers should be practically considered. Paradoxically and despite the observable social fear of ESRD, which may progress up to a disease phobia in developing countries[45], there are many patient-related factors that influence early diagnosis and management of

Table 6 Frequency of preemptive living donor kidney transplantation in publications from other countries/registries, *n* (%)

Ref.	Countryand/or Registry	Total KT Number	PKT	LDKT number (Percentage of PLDKT)	PKT per donor type	
					LD	DD
Migliori <i>et al</i> [19]	United States	1742	132 (7.6%)	1056 (9.1)	96 (73)	36 (27)
Berthouix <i>et al</i> [20]	ERA-EDTA	35348	2545 (7.2)	1097 (73.3)	804 (31.6)	1741 (68.4)
Asderakis <i>et al</i> [21]	United Kingdom	1463	161 (11)	118 (19.5)	23 (14)	138 (86)
Papalois <i>et al</i> [22]	United States	1849	385 (20.8)	1074 (29.1)	313 (81.3)	72 (18.7)
¹ Mange <i>et al</i> [23]	United States; USRDS	8489	1819 (21.4)	1819 (21.4)	1819 (100)	NA
Kasiske <i>et al</i> [24]	United States; UNOS	38836	5126 (13.2)	13078 (24)	3145 (61.4)	1981 (38.6)
Gill <i>et al</i> [25]	Canada; CORR	40963	5996 (14.6)	11290 (26.6)	2999 (50.5)	2967 (49.5)
Ashby <i>et al</i> [26]	United States; OPTN/SRTR	102331	17885 (17.5)	44033 (26.3)	11601 (65)	6284 (35)
¹ Ishikawa <i>et al</i> [27]	Japan; JRTR	834	112 (13.4)	834 (13.4)	112 (100)	NA
¹ Milton <i>et al</i> [28]	ANZDATA	2603	578 (22)	578 (22)	578 (100)	NA
¹ Yoo <i>et al</i> [29]	Korea	499	81 (16.2)	499 (16.2)	81 (100)	NA
Gore <i>et al</i> [30]	United States; UNOS	41090	11026 (26.8)	15940 (39.4)	6282 (57)	4744 (43)
Witczak <i>et al</i> [31]	Norway	3400	809 (24)	1415 (36.3)	514 (64)	295 (36)
² Kramer <i>et al</i> [32]	ERA-EDTA	1829	444 (21.2)	1073 (11.5)	123 (72)	321 (28)
Grams <i>et al</i> [33]	United States; UNOS	152731	19471 (12.8)	NA	11554 (59)	7917 (41)
¹ Grace <i>et al</i> [34]	ANZDATA	4105	660 (16.1)	2058 (16.1)	660 (100)	NA
² Patzer <i>et al</i> [35]	United States; USRDS	5774	1117 (19.3)	2598 (28.8)	747 (67)	370 (33)
Jay <i>et al</i> [2]	United States; UNOS	141254	24609 (17)	46373 (31)	14503 (59)	10106 (41)
Prezelin-Reydit <i>et al</i> [36]	France; REIN	22345	3112 (14)	2031 (34)	690 (22.2)	2422 (77.8)
¹ Kim <i>et al</i> [37]	South Korea	1984	429 (21.6)	1984 (21.6)	429 (100)	NA
² Prezelin-Reydit <i>et al</i> [38]	France; REIN	1911	380 (19.8)	240 (37.5)	90 (23.7)	290 (76.3)

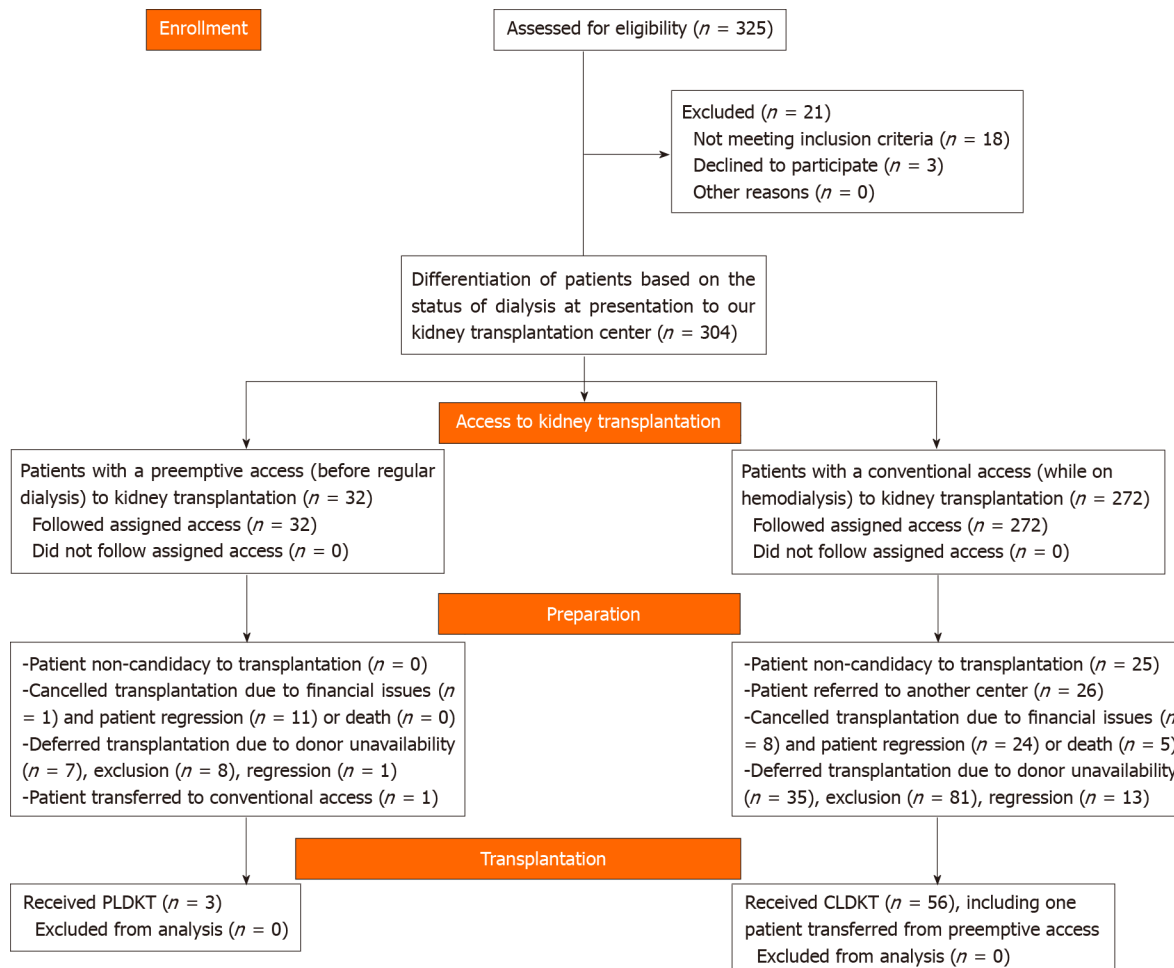
¹Studies included only living donor kidney transplantation.²Studies included only pediatric kidney transplantation.

ANZDATA: Australia and New Zealand Dialysis and Transplant Registry; CORR: Canadian Organ Replacement Registry; DD: Deceased donor; ERA-EDTA: European Renal Association-European Dialysis and Transplant Association; JRTR: Japanese Renal Transplant Registry; LD: Living donor; LDKT: Living donor kidney transplantation; PKT: Preemptive kidney transplantation; PLDKT: Preemptive living donor kidney transplantation; N/A: Not applicable; OPTN/SRTR: Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients; REIN: Renal Epidemiology and Information Network; UNOS: United Network for Organ Sharing; USRDS: United State Renal Data System.

CKD patients such as the cultural and health illiteracies[44]. As a developing country, the healthcare authorities in Egypt have a large burden of challenges which seem hard to be overcome due to factors such as low per-capita income and slowly progressing corrections of the healthcare systems[15]. Also, the ethical problems that have been raised about KT practice in Egypt represent another major confounder to correction[46]. However, the recent policies in the Egyptian national healthcare system seem to be promising as a mass modification to overcome these problems, including the new national health insurance coverage and national KT programs.

The limitations of the current study included the small number of patients who had PLDKT, which made us unable to perform statistical analyses for the independent factors of failure of most patients with PAKT to achieve PLDKT. However, this is the first study from Egypt to address this very viable topic at a national review basis. Hence, it may unmask the vague situation of PLDKT in Egypt by configuring a step forward in building more integrated KT systems.

Based on relevant literature review, we may recommend implementation of different strategies to promote PLDKT in Egypt. Encouragement of LKD is the main strategy that should be extensively studied, because our national KT program is currently devoted to LDKT only. Minimally-invasive approaches such as laparoscopic living donor nephrectomy should be introduced to all centers of KT. Also, the regulations of LKD should be organized under a well-configured national donation program,



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Figure 1 Flowchart of patients who accessed our center seeking living donor kidney transplantation. Relative to the status of dialysis at access, this chart shows the steps through which the patients and their potential donors were evaluated to achieve kidney transplantation. CLDKT: Conventional living donor kidney transplantation; PLDKT: Preemptive living donor kidney transplantation.

including donor exchange programs. Furthermore, promotion of healthcare facilities of early detection of CKD and education of the contributors of PLDKT process are crucial strategies for this topic. The latter includes the education of the physicians (representing the moderator of the process), ESRD patients (representing the key start of the process), and publics (representing the source of the potential donors) about the benefits of PKT.

CONCLUSION

Patients with PAKT may have significant differences from those with CAKT regarding age, sex, primary kidney disease, and number of potential donors at presentation to a KT center. A primary kidney disease diagnosis is an independent factor of achievement of LDKT. In addition, older age and female sex are independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of LDs and patient regression when reach dialysis may hinder the achievement of PLDKT in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable or slightly better outcomes than those of CLDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, PLDKT may have similar barriers to those presented elsewhere in the literature, including the shortage of donors, delayed presentation of patients and socioeconomic factors. As a result, the rate of PLDKT is still low in Egypt, warranting implementation of many strategies to promote PLDKT. They include encouraging LKD, introduction of minimally-invasive living donor nephrectomy, configuring a specific program for LKD, and education of the physicians, patients and publics about the benefits of PKT.

ARTICLE HIGHLIGHTS

Research background

Despite its low rates, preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease. However, its rate is still lower than the expected rates worldwide.

Research motivation

Promotion of the rate of PLDKT seems to be a modifiable variable for improvement of the total outcomes of KT.

Research objectives

To assess the rate of achievement of PLDKT among patients accessing KT in our center and to review the status of PLDKT in Egypt in the context of the international literature.

Research methods

We performed a retrospective review of the records of patients who accessed KT in our center from November 2015 to November 2022. The demographic and clinical characteristics of the patients and their potential donors were reviewed. Also, the literature was reviewed for PLDKT status in Egypt.

Research results

Of 304 patients accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were 31.7 ± 13 years and 12.8 ± 3.5 mL/min/1.73 m², respectively. Fifty-nine patients had KT, including three PLDKTs only (5.1% of the total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (39.3%). In multivariate analysis, known primary kidney disease ($P = 0.002$), patient age ($P = 0.031$) and sex ($P = 0.001$) were independent predictors of achievement of KT in our center. However, PAKT was not significantly ($P = 0.065$) associated with the achievement of KT. Review of the literature revealed lower rates of PLDKT in Egypt, including the current results, than the internationally reported rates.

Research conclusions

Patient age, sex, and primary kidney disease are independent predictors of achieving LDKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

Research perspectives

Studying the factors that may promote the early access of ESRD patients to KT may improve the rates of PLDKT. This latter strategy may improve the whole outcomes of the process of KT, including avoidance of the inconveniences of dialysis and improvement of the graft and patient survival rates.

FOOTNOTES

Author contributions: Gadelkareem RA, Abdelgawad AM, and Zarzour MA designed the research, collected the data, and wrote the paper; Reda A, Azoz NM, and Mohammed N contributed to the statistical analysis, literature review, writing and revision; Hammouda HM and Khalil M contributed to the literature review, writing, revision and supervision of the work; All authors approved the paper.

Institutional review board statement: This study has been approved in 2017 by the Medical Ethics Committee of the Faculty of Medicine, Assiut University, Egypt as a topic in a research project titled "Outcome of living donor kidney transplantation in Assiut Urology and Nephrology Hospital". The institutional review board number is 17200148.

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

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: The data supporting this study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was

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Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise

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Abstract

BACKGROUND

There are two known types of exercise-induced acute renal failure. One is the long-known myoglobinuria-induced acute renal failure due to severe rhabdomyolysis, and the other is the recently recognized non-myoglobinuria-induced acute renal failure with mild rhabdomyolysis. Exercise-induced acute renal failure was first reported in 1982. Non-myoglobinuria-induced acute renal failure is associated with severe low back pain and patchy renal vasoconstriction, and it is termed post-exercise acute renal failure because it usually occurs hours after exercise. It is also called acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE).

AIM

To make a significant contribution to medical literature as it presents a study that investigated a not-widely-known type of exercise-induced acute renal failure known as ALPE.

METHODS

We performed a database search selecting papers published in the English or Japanese language. A database search was lastly accessed on September 1, 2022. The results of this study were compared with those reported in other case series.

RESULTS

The study evaluated renal hypouricemia as a key risk factor of ALPE. The development of ALPE is due to the sum of risk factors such as exercise, hypouricemia, nonsteroidal anti-inflammatory drugs, vasopressors, and dehydration.

CONCLUSION

In conclusion, hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise. The development of ALPE is a result of the cumulative effects of risk factors such as exercise, hypouricemia, NSAIDs, vasopressors, and dehydration.

Key Words: Acute kidney injury; Exercise; Vasoconstriction; Renal hypouricemia

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Core Tip: Exercise is important for health maintenance and promotion. However, exercise-induced acute renal failure is a disease that athletes and doctors should be aware of. This paper makes a significant contribution to medical literature as it presents a study that investigated a not-widely-known type of exercise-induced acute renal failure known as Acute renal failure with severe Loin pain and Patchy renal ischemia after anaerobic Exercise (ALPE). Further, the study evaluated renal hypouricemia as a key risk factor of ALPE. The information in this paper can help clinicians make more accurate diagnosis, given that a significant proportion of patients with ALPE are undiagnosed. Further, this paper can increase awareness among athletes to help them prevent ALPE and reach their exercise goals.

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INTRODUCTION

There are two known types of exercise-induced acute renal failure (ARF). One is the long-known myoglobinuria-induced ARF due to severe rhabdomyolysis, and the other is the recently recognized non-myoglobinuria-induced ARF with mild rhabdomyolysis. The distinguishing features of the two types of exercise-induced ARF are summarized in [Table 1](#).

Exercise-induced ARF was first reported by Ishikawa in 1982. Non-myoglobinuria-induced ARF is associated with severe low back pain and patchy renal vasoconstriction, and it is termed post-exercise ARF because it usually occurs hours after exercise. It is also known as ARF with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE)[1].

Recently, many reports of post-exercise ARF, especially in patients with renal hypouricemia, have attracted attention. Thus, in this study, we report on the types of ALPE.

MATERIALS AND METHODS

Clinical findings in patients with ALPE

We searched PubMed for studies on ALPE and summarized 57 reported cases of ALPE, including self-examination cases[2-29] ([Figure 1](#)). The following patient characteristics were investigated: Sex, age at ARF episode, past history, first symptom of the ARF episode, type of exercise leading to ARF, date of ARF episode, first examination data of the ARF episode, baseline levels of uric acid, and treatment of ARF.

Comparison of the characteristics of patients with ALPE

The results of this study were compared with those reported in other case series[30,31].

Comparison of the characteristics of patients with ALPE with and without renal hypouricemia

We compared the characteristics of patients with ALPE and renal hypouricemia with those of patients with ALPE without renal hypouricemia.

Interstudy comparison of the characteristics of patients with ALPE

The characteristics of patients with ALPE with and without renal hypouricemia were compared with those reported in other case series[32].

RESULTS

Clinical findings in patients with ALPE

We summarized 57 reported cases of ALPE, including self-examination cases ([Table 2](#)). ALPE most

Table 1 Differential diagnosis of acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise and myoglobinuria acute renal failure

	ALPE	Myoglobinuria acute renal failure
Amount of exercise	+	+++
Type of exercise	Anaerobic exercise	Aerobic exercise
Urine volume	Non-oliguria	Oliguria
Reddish brown urine	-	+++
Loin pain	+++	-~+
Nausea, vomiting/slight fever	++	+-
Dehydration	+	+++
Serum CK/serum myoglobin	normal or mildly elevated	↑↑↑

ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CK: Creatinine kinase.

Table 2 Clinical findings in 57 patients with acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise, *n* (%)

Age (yr)	22.09 ± 9.55 (13-65)
Sex	Male 52 (91.2%), female 5 (8.8%)
Exercise	47/57 (82.5)
Fever	19/57 (33.3)
Nausea/vomiting	36/57 (63.2)
Loin pain	36/57 (63.2)
Abdominal pain	32/57 (56.1)
High blood pressure on admission	10/30 (33.3)
High CRP on admission	13/18 (72.2)
Serum creatinine on admission (mg/dL)	4.81 ± 2.25 (1.08-12.1), <i>n</i> = 56
Serum myoglobin on admission (ng/mL)	86.46 ± 66.80 (10-260), <i>n</i> = 21
Serum CK on admission (IU/L)	272.76 ± 301.97 (38-1182), <i>n</i> = 47
Kidney CT patchy findings	32/40 (80)
Hemodialysis	10/54 (18.5)
Hydration	37/54 (68.5)
Hydration+drugs	6/54 (11.1) [furosemide (2), dopamine (2), nicardipine (1), Vitamin C, E (1)]
Rest	1/54 (1.9)
Renal hypouricemia	31/57 (54.4)
Recurrence of ALPE	14/54 (25.9)
Days of renal failure improvement	17.4 ± 10.4 (d), <i>n</i> = 35
Premedication	5/26 (19) [vasopressor (2), NSAIDs (1), Antibiotic agent (1), epileptic drugs (1)]

Values are expressed with mean ± standard deviation with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CRP: C-reactive protein; CK: Creatinine kinase; CT: Computed Tomography; NSAIDs: Non-steroidal anti-inflammatory drugs.

commonly occurs post-exercise (82.5%) and in men (91.2%). In addition to back pain (63.2%) at the first hospital visit, many patients with ALPE present with abdominal pain (56%), vomiting (63.2%), mild fever (33.3%), and high C-reactive protein (CRP) levels (72.2%).

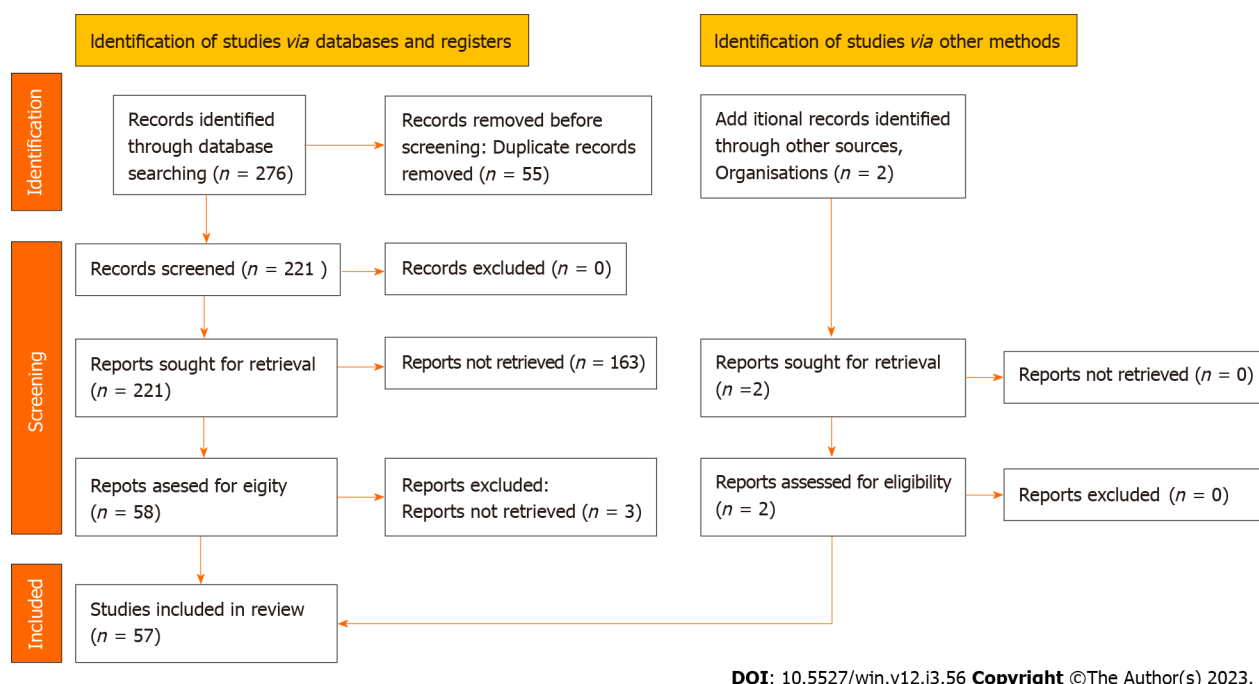


Figure 1 PRISMA flow diagram.

Wedge-shaped scars were noted on contrast-enhanced computed tomography (CT) in 80% of the cases. The mean serum creatinine, creatine phosphokinase, and myoglobin levels at initial presentation were 4.81 mg/dL, 272 IU/L, and 86 ng/mL, respectively. Moreover, most of the patients (68.5%) only received hydration therapy, 18.5% of the patients underwent hemodialysis (HD), and only a few patients were treated with oral medications. The mean recovery period was approximately 17 d, 25.9% of the patients had ALPE recurrence, and 54.4% of the patients presented with hypouricemia.

Comparison of the characteristics of patients with ALPE

The results of this study were comparable with those of the other case series (Table 3).

Comparison of the characteristics of patients with ALPE with and without renal hypouricemia

Table 4 shows the comparison of the characteristics of patients with ALPE with and without renal hypouricemia. The mean duration of acute kidney injury with hypouricemia was 17.9 d, whereas that of acute kidney injury without hypouricemia was 16.1 d. Overall, 24% of patients underwent HD, 12% of whom did not have hypouricemia. ALPE recurrence with hypouricemia was observed in 39% of patients and that without hypouricemia in 12% of the patients.

Interstudy comparison of the characteristics of patients with ALPE

The findings of this study were consistent with those of previous studies (Table 5).

DISCUSSION

Clinical features of ALPE

The clinical features of ALPE are as follows[33]: ARF (A), severe back (loin) pain (L), and patchy renal ischemia of acute onset (P) after anaerobic exercise (E). Most patients with ALPE (approximately 90%) are men, and the age of onset is as low as 15-17 years. Most cases have been reported so far in Japan, and the relationship between ALPE and renal hypouricemia has attracted attention. Some patients administered antipyretic analgesics before exercise and had a slight cold. The risk factors for ALPE are summarized below.

Exercise: The types of exercises include anaerobic and repeated anaerobic exercises, such as track and field (sprinting), soccer, muscle training, swimming, cycling, baseball, and weightlifting. ALPE most commonly occurs after sprinting 200 m multiple times at sports festivals[34].

Loin pain: Loin pain refers to severe pain that seems to originate from the kidney, rather than from the muscles of the extremity used during exercise. It occurs 1-48 h (typically 3-12 h) after exercise. The pain is bilateral and mostly described as back pain, but it is occasionally described as abdominal, low back, or

Table 3 Comparison of characteristics in acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise, *n* (%)

	This cases	Ohta et al[31], 2004	Ishikawa et al[30], 2002
Age (yr)	22.1 ± 9.6 (13-65)	19.3 ± 8.1 (11-46)	22.0 ± 7.6 (10-54)
Sex (male)	52/57 (91.2)	48/54 (88.9)	112/118 (94.9)
Fever	19/57 (33.3)	7/60 (11.7)	38/47 (80.9)
Nausea/vomiting	36/57 (63.2)	51/60 (85)	84/88 (95.5)
Loin pain	36/57 (63.2)	35/60 (58.3)	NA
Abdominal pain	32/57 (56.1)	22/60 (36.7)	NA
Serum creatinine on admission (mg/dL)	4.81 ± 2.52 (N = 56)	NA	4.70 ± 2.90 (N = 77)
Kidney CT patchy findings	32/40 (80)	NA	49/96 (92)
Hemodialysis	10/54 (18.5)	NA	20/118 (16.9)
Exercise	47/57 (82.5)	61/61 (100)	118/118 (100)
Renal hypouricemia	31/57 (54.4)	48/48 (100)	49/96 (51)
Recurrence of ALPE	14/54 (25.9)	13/54 (24.1)	20/118 (16.9)
Days of renal failure improvement	17.4 ± 10.4 (N = 35)	NA	13.1 ± 8.3 (N = 87)

Values are expressed with mean ± standard deviation with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CT: Computed Tomography; N: Number of patients; NA: Not available.

flank pain.

High pain severity does not allow patients with loin pain to drive a car. In addition, the patients complain of nausea, vomiting, and abdominal pain. They present to the hospital with mild fever and slightly high CRP levels.

Renal hypouricemia: Patients with ALPE and renal hypouricemia typically have more frequent relapses, more severe ARF, and longer recovery periods than those with ALPE and no renal hypouricemia. Since the identification of the gene for renal hypouricemia in Japan[35], post-exercise ARF has been gaining popularity as a complication of renal hypouricemia.

Clinically misdiagnosed diseases: ALPE may include clinically misdiagnosed diseases, such as urinary tract stones, acute gastroenteritis, acute pancreatitis, acute glomerulonephritis, acute pyelonephritis, and lumbago.

Diagnostic method: Having sufficient knowledge of ALPE is the first step in its diagnosis. A considerable number of ALPE cases may remain undiagnosed and are overlooked. It is important to obtain a medical history of exercise, especially anaerobic exercise, for accurate diagnosis of ALPE.

Diagnostic criteria

(1) History of repeated anaerobic exercise or exercise set that includes anaerobic exercise; (2) Back pain experienced 1-48 h (typically 3-12 h) after exercise; (3) Normal or slightly elevated serum creatine kinase (CK) levels (serum CK levels that are ≤ 9 times the reference value and serum myoglobin levels that are ≤ 7 times the reference value); and (4) Wedge-shaped residual contrast medium observed on delayed CT (1-2 d after the administration of the contrast medium) when the serum creatinine level is 1.2-3.5 mg/dL. ARF with criteria (1) to (3) is required for the diagnosis of ALPE; however, criterion (4) is not required for clinical diagnosis[33]. In rare cases, patients do not complain of back pain or remember exercising. These cases are considered atypical.

In atypical cases of ALPE, urinalysis does not show reddish-brown urine, patients usually have nonoliguric ARF, and oliguria is rare. The level of fractional excretion of sodium fluctuates between < 1% and > 1%. Furthermore, proteinuria and hematuria may be positive or negative, and the result of urinalysis is not definitive. Dehydration is rare, and the blood pressure level at the time of admission is usually normal.

Treatment: A considerable number of patients with low back pain several days after a sports festival may be overlooked without a diagnosis of ALPE who ultimately heal spontaneously. If a patient with ALPE presents to an emergency department with pain, nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered without consideration. This is because NSAIDs may exacerbate ARF,

Table 4 Comparison of characteristics in acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise with and without renal hypouricemia, n (%)

	Renal hypouricemia	No renal hypouricemia
Number of patients	31	26
Age (yr)	21.6 ± 10.7 (11-65)	22.7 ± 8.0 (13-49)
Sex (male)	28/31 (90)	24/26 (92)
fever	7/31 (23)	12/26 (46)
Nausea/vomiting	22/31 (71)	14/26 (54)
Loin pain	21/31 (68)	15/26 (58)
Abdominal pain	14/31 (45)	18/26 (69)
High blood pressure on admission	6/21 (28.6)	4/9 (44.4)
High CRP on admission	9/14 (64.3)	4/4 (100)
Serum creatinine on admission (mg/dL)	4.53 ± 2.04 (N = 30)	5.24 ± 2.81 (N = 26)
Serum CK on admission (IU/L)	261 ± 304 (N = 26)	269 ± 225 (N = 21)
Kidney CT patchy findings	9/15 (60)	23/25 (92)
Hemodialysis	7/29 (24)	2/25 (8)
Exercise	29/31 (94)	19/26 (73)
Recurrence of ALPE	11/28 (39)	3/26 (12)
Days of renal failure improvement	17.9 ± 8.3 (N = 26)	16.1 ± 15.3 (N = 10)
premedication	2/20 (10)	3/6 (50)

Values are expressed with mean ± standard deviation with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CRP: C-reactive protein; CK: Creatinine kinase, CT: Computed Tomography; N: Number of patients.

Table 5 Comparison of characteristics in acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise with and without renal hypouricemia, n (%)

	Renal hypouricemia, this cases	Renal hypouricemia, Ishikawa[32], 2014	No renal hypouricemia, this cases	No renal hypouricemia, Ishikawa[32], 2014
Number of patients	31	148	26	94
Age (yr) median	18 (11-65)	18 (15-25)	21 (13-49)	19 (16-26)
Sex (male)	28/31 (90)	136/148 (92)	24/26 (92)	82/92 (89)
Fever	7/31 (23)	35/43 (81)	12/26 (46)	35/49 (71)
Nausea/vomiting	22/31 (71)	106/107 (99)	14/26 (54)	63/66 (95)
Serum CK on admission (IU/L)	155 (44-1182), N = 26	212 (100-447), N = 81	225 (38-686), N = 21	317 (124-696), N = 70
Serum creatinine on admission (mg/dL)	4.2 (1.1-8.9), N = 30	4.3 (2.6-6.7), N = 122	4.7 (1.4-7.6), N = 26	3.2 (2-5.1), N = 75
Kidney CT patchy findings	9/15 (60)	31/32 (97)	23/25 (92)	56/58 (97)
Hemodialysis	7/29 (24)	46/148 (31)	2/25 (8)	16/94 (17)
Recurrence of ALPE	11/28 (39)	38/148 (26)	3/26 (12)	7/94 (7)
Days of renal failure improvement (d)	17 (6-30), N = 26	14 (10-19), N = 85	15 (5-22), N = 10	10 (7-16), N = 66

Values are expressed with median with (range) or the number of positive cases with (percent). ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; CK: Creatinine kinase; CT: Computed Tomography; N: Number of patients.

leading to oliguria and the need for dialysis therapy. If analgesia is considered necessary, centrally administered analgesics should be used instead of NSAIDs. The treatment is initially conservative. Hydration should be normal, and body weight should be maintained at the presymptomatic value. Regarding fluid balance, body weight should be controlled to the standard value with fluid replacement in cases of dehydration, and diuretics should be administered in cases of excess body fluid. Dialysis therapy is rarely used for treating oliguria, uremia, hyperkalemia, and heart failure.

Prevention: The management of patients with renal hypouricemia (particularly those with serum uric acid levels of ≤ 1 mg/dL) is an issue at school club activities and sports festivals. As ALPE recurs easily, patients with a history of ALPE should be advised to be wary of dehydration and of types of exercise likely to induce ALPE. These patients should also be advised to take preventive steps such as avoiding exercises that induce ALPE. However, there is yet no established definitive prevention method against ALPE recurrence. There is insufficient evidence to prove that drugs suppressing the generation of reactive oxygen species, such as allopurinol and vitamins A, C, and E, prevent ALPE[1].

Pathogenesis of ALPE

The pathophysiological mechanism of ALPE is unknown, but renal circulatory impairment due to reactive oxygen species (ROS) is believed to be the main cause of ALPE[36].

Strenuous exercise, such as anaerobic exercise, generates large amounts of ROS, which are rapidly cleared by uric acid, a potent ROS scavenger, and other scavengers in healthy populations[37]. Consequently, patients with renal hypouricemia have insufficient scavengers, leading to inadequate ROS clearance, resulting in the activation of vasoconstrictors, vasoconstriction, and renal ischemia[31].

As renal vasoconstriction is known to cause further vasoconstriction and oxidative stress *via* the activation of the renin-angiotensin system as well as increased blood pressure level[38], patients with ALPE may be in a vicious cycle of oxidative stress and vasoconstriction. Oxidative stress causes stronger vasoconstriction, which in turn causes more oxidative stress, leading to acute ischemia and severe renal damage. The ischemia is localized to the kidney, but on rare occasions, it spreads to other organs. In extremely rare cases, it is accompanied by a spasm of the cerebral vessels, resulting in reversible occipital lobe leukoencephalopathy[39].

Genetic abnormalities in patients with renal hypouricemia who develop ALPE include mutations in the uric acid transporter *URAT1*, homozygotes for W258X, and compound heterozygotes including *URAT1* and W258X. Homozygotes for R90H have also been reported[40].

Based on these findings, hypouricemia, rather than genetic mutation, is considered a risk factor for ALPE. In fact, patients with renal hypouricemia are approximately 50 times more likely to develop ALPE than those with nonrenal hypouricemia[32].

The case of a patient with ALPE without exercise who had no episodes of strenuous exercise was recently reported by Lee *et al*[29]. However, enhanced CT revealed characteristic patchy renal signs.

To the best of our knowledge, 10 patients with ALPE without an episode of strenuous exercise have been reported so far, 8 of whom had an infection or took a vasopressor or analgesic before the onset of ALPE. Moreover, infection and vasopressor and analgesic use are considered as risk factors for ALPE (Table 6)[3,12,28,31].

The abovementioned reports suggest that ALPE can develop without strenuous exercise or other risk factors.

Aomura *et al*[3] reported ALPE in a patient who took vasopressors for orthostatic dysregulation for 15 days before the onset of ALPE.

It is possible that vasopressors induced or exacerbated ALPE by increasing ROS levels, worsening vasoconstriction, and forming a vicious cycle of decreased renal hemodynamics.

Karasawa *et al*[17] reported the case of a patient who was administered the vasoconstrictor midodrine before the onset of ALPE.

Radaković *et al*[41] demonstrated that vasodilation with low-dose dopamine improved the renal arteriolar resistance index in two cases of ALPE, suggesting a relationship between vasopressors and ALPE in clinical settings.

No study has directly addressed the relationship between vasopressors and ALPE; however, previous studies have shown the importance of catecholamine level homeostasis in the pathogenesis of ALPE. Vasopressors may be associated with the development of ALPE in patients with hypouricemia and may be a risk factor for ALPE.

CONCLUSION

In conclusion, hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise. The development of ALPE is a result of the cumulative effects of risk factors such as exercise, hypouricemia, NSAIDs, vasopressors, and dehydration.

Table 6 Clinical findings of current and previous reported cases of acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise without strenuous exercise

Patient No.	Age (yr)	Sex	Renal hypouricemia	Suspected trigger
1	14	Male	Yes	Gastroenteritis
2	30	Male	Yes	NA
3	33	Male	NR	URI and heavy alcoholconsumption
4	23	Female	NR	URI
5	25	Male	No	URI
6	32	Male	No	NSAIDs
7	30	Male	NR	NA
8	49	Male	Yes	Coincidence of myalgia
9	15	Male	Yes	Vasopressor
10	65	Male	Yes	Ureteral stone and NSAIDs

ALPE: Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise; NA: Not available; URI: Upper respiratory infection; NSAIDs: Non-steroidal anti-inflammatory drugs.

ARTICLE HIGHLIGHTS

Research background

Recently, many reports of post-exercise acute renal failure, especially in patients with renal hypouricemia, have attracted attention. The pathophysiological mechanism of acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE) is unknown, but renal circulatory impairment due to reactive oxygen species is believed to be the main cause of ALPE. Hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise.

Research motivation

Exercise is important for health maintenance and promotion. However, exercise-induced acute renal failure is a disease that athletes and doctors should be aware of.

Research objectives

This paper makes a significant contribution to medical literature as it presents a study that investigated a not-widely-known type of exercise-induced acute renal failure known as ALPE.

Research methods

We performed a database search selecting papers published in the English or Japanese language. A database search was lastly accessed on 1 September 2022. The results of this study were compared with those reported in other case series.

Research results

The study evaluated renal hypouricemia as a key risk factor of ALPE. The development of ALPE is due to the sum of risk factors such as exercise, hypouricemia, nonsteroidal anti-inflammatory drugs, vasopressors, and dehydration.

Research conclusions

Hypouricemia plays a key role in the development of ALPE and is often associated with anaerobic exercise. The development of ALPE is a result of the cumulative effects of risk factors such as exercise, hypouricemia, NSAIDs, vasopressors, and dehydration.

Research perspectives

The information in this paper can help clinicians make more accurate diagnosis, given that a significant proportion of patients with ALPE are undiagnosed. Further, this paper can increase awareness among athletes to help them prevent ALPE and reach their exercise goals.

FOOTNOTES

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Infection related membranoproliferative glomerulonephritis secondary to anaplasmosis: A case report

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Abstract

BACKGROUND

Anaplasmosis is a tick-borne disease with a range of clinical manifestations, from a flu-like illness with fever and myalgias to a severe systemic disease with multisystem organ failure. Although renal involvement is not a common presentation, there have been few cases reporting acute kidney injury from Anaplasmosis.

CASE SUMMARY

We present a 55-year-old female with anaplasmosis who developed acute kidney injury due to membranoproliferative glomerulonephritis (MPGN). The patient originally presented with cough and shortness of breath. She was admitted to the hospital with a diagnosis of community acquired pneumonia and received antibiotics. During the hospital course she developed severe acute renal failure. Initial serological work up didn't provide any conclusive diagnosis. Hence, she underwent kidney biopsy which showed MPGN pattern suggesting autoimmune, multiple myeloma or infectious etiology. Extensive work up was undertaken which was negative for autoimmune diseases, vasculitis panel, paraproteinemias but tested positive for IgG anaplasma with high titers indicating Anaplasmosis.

CONCLUSION

Our case shows a unique presentation of severe acute renal failure from MPGN from tick borne illness. MPGN is usually seen with autoimmune diseases, hepatitis C virus infections, paraproteinemias. Hence, we suggest that tick borne illness should also be considered when evaluating acute renal failure cases in tick borne prevalent regions.

Key Words: Acute kidney injury; Membranoproliferative glomerulonephritis; Tick-borne; Anaplasmosis; Case report

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Core Tip: In areas endemic for tick borne illnesses, it is important to learn and understand common and rare presentations of tick borne illness. Our case is unique as it showed that tick borne illness can also cause severe renal failure by inciting Glomerulonephritis which is usually seen with other etiologies but very rarely with Anaplasmosis.

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INTRODUCTION

Human granulocytic anaplasmosis (HGA) is a tickborne rickettsial disease caused by the bacterium *Anaplasma phagocytophilum*. It is a gram-negative intracellular bacterium transmitted by *Ixodes scapularis* tick. Typical symptoms of HGA include fever, malaise, headache, myalgias, and occasionally arthralgias[1]. We report a case that presented with cough, shortness of breath and acute kidney injury. Only 17 of the 110 reported patients of anaplasmosis had acute kidney injury[1]. To the best of our knowledge, this is the first report of a membranoproliferative glomerulonephritis (MPGN) nephritic pattern of acute kidney injury seen in a HGA infection.

CASE PRESENTATION

Chief complaints

A 55-year-old female presented to the Emergency Department with cough and shortness of breath that had persisted for three days.

History of past illness

The patients' medical history was pertinent for liver cirrhosis secondary to alcohol abuse, ascites requiring weekly paracentesis, chronic hyponatremia secondary to cirrhosis, chronic antibiotics for spontaneous bacterial peritonitis prophylaxis, and hypertension.

Physical examination

After evaluation, there was a concern for pneumonia, based on the basic laboratory tests and a chest x-ray. Her initial vitals were: 104 beats per minute heart rate, 28 per minute respiratory rate, 36.5 degrees Celsius temperature, 128/63 mmHg blood pressure, and 92%SpO₂ on presentation to the emergency department. A complete physical examination revealed only significant rales in the left lower lung.

Laboratory examinations

Her coronavirus disease 2019 polymerase chain reaction (PCR) resulted negative (Tables 1 and 2).

Imaging examinations

Chest x-ray showed bilateral patchy opacities and a subsequent computed tomography (CT) scan was performed, revealing pneumonia-like findings.

FINAL DIAGNOSIS

MPGN secondary to Anaplasmosis.

Table 1 Summary of key diagnostic tests

Diagnostic Test	Normal value	Result
ANA	Negative	Negative
Serum DNA double-stranded antibody, IgG	< 30.0 (Negative) IU/mL	< 12.3
Glomerular basement membrane IgG antibody	< 1.0 (Negative) U	< 0.2
Serum myeloperoxidase antibody	< 0.4 (Negative) U	< 0.2
Serum proteinase 3 antibody (PR3)	< 0.4 (Negative) U	< 0.2
Serum complement C3	75-175 mg/dL	42
Serum complement C4	14-40 mg/dL	8
Serum haptoglobin	30-200 mg/dL	17
Serum kappa free light chain	0.3300-1.94 mg/dL	9.28
Serum lambda free light chain	0.5700-2.63 mg/dL	10.9
Kappa/lambda FLC ratio	0.2600-1.65	0.8514
Serum protein electrophoresis	Negative monoclonal proteins	Negative monoclonal proteins
Serum antistrept-O titer	0-530 IU/mL	69
Blood culture	Negative	Negative
Urine culture	Negative	Negative
SARS-CoV-2, PCR, rapid	Undetected	Undetected
EBV DNA, P	Undetected	Undetected
CMV DNA, P	Undetected	Undetected
Anaplasma phagocytophilum, PCR	Undetected	Undetected
Serum Anaplasma phagocytophilum antibody, IgG	< 1:64 titer	1:512
Ehrlichia chaffeensis, PCR	Negative	Negative
Ehrlichia chaffeensis (HME) antibody, IgG	< 1:64	< 1:64
Bartonella antibody panel, IgG and IgM	Negative	Negative
Serum Blastomyces antibody, EIA	Negative	Negative
Histoplasma antibody	Negative	Negative
HIV -1 Ab Screen, P	Negative	Negative
HIV-1 p24 Ag Screen, P	Negative	Negative
HIV Ag/ Ab Screen, P	Negative	Negative
HIV-2 Ab Screen, P	Negative	Negative
Serum Mycoplasma antibody, IgM	Negative	Negative
Serum Mycoplasma antibody, IgG	Negative	Positive
Serum total hepatitis B core antibody	Negative	Negative

HIV: Human immunodeficiency virus; ANA: Serum antinuclear antibody; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PCR: Polymerase chain reaction; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; FLC: Free light chains.

TREATMENT

She was admitted to the hospital and started on empiric antibiotics for community-acquired pneumonia with cefepime and metronidazole. Her baseline creatinine was 0.6 to 1 mg/dL but during the hospital course she developed an acute kidney injury, with her creatinine reaching 1.6 mg/dL. Her acute kidney injury was thought to be caused by hepatorenal syndrome. She received albumin, midodrine, and octreotide.

Table 2 Laboratory test results

Diagnostic test	Normal value	At presentation	Hospital day 2	Hospital day 6	Hospital day 11	Hospital day 15	On discharge
Hemoglobin, g/dL	11.6-15.0	8.9	8	9.1	9	6.8	7.3
WBC count, $\times 10^9$ /L	3.4-9.6	15.5	16.2	16.8	12.6	8.1	9.2
Platelet count, $\times 10^9$ /L	157-371	118	105	168	157	115	124
Serum Urea Nitrogen, mg/dL	45098	31	36	55	46	66	87
Serum creatinine, mg/dL	0.59-1.04	1.62	1.84	1.02	1.55	2.87	2.95
Serum sodium	135-145 mmol/L	124	123	129	126	127	135
Serum potassium	3.6-5.2 mmol/L	4.5	4.3	3.7	3.8	3.8	4
Serum chloride	98-107 mmol/L	102	100	105	95	95	100
Serum bicarbonate	22-29 mmol/L	11	11	10	20	20	20
eGFR	≥ 60 mL/min/BSA	35	30	62	37	18	17
Anion gap	45122	11	12	12	9	12	15
Serum calcium	8.6-10.0 mg/dL	7.7	7.3	7.8	7.2	7.3	7.6
Serum albumin	3.5-5.0 g/dL	1.6		1.4	1.8		

WBC: White blood cell; eGFR: Estimated glomerular filtration rate; BSA: Body surface area.

OUTCOME AND FOLLOW-UP

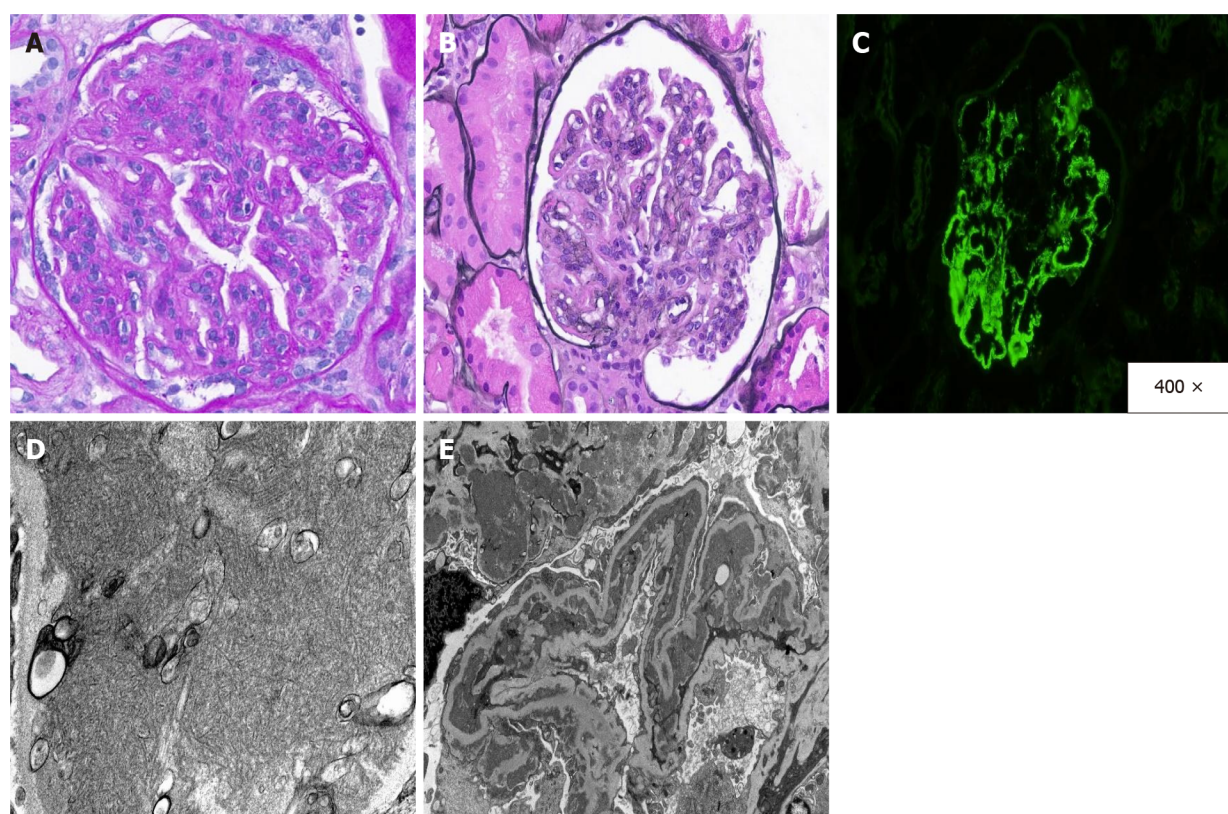
On day 5, she underwent paracentesis due to underlying alcoholic liver cirrhosis with ascites. The paracentesis cultures were negative. On day 6, renal function recovered to baseline, but the leukocyte count remained persistently elevated, despite empirical treatment with cefepime and metronidazole. Her respiratory status did not improve, and a repeat chest CT was performed on day 7, revealing persistent bilateral opacities. Concurrently, her leukocytosis was worsening. Pulmonology was consulted and they have recommended diuresis to relieve the fluid overload and also recommended getting an echocardiogram. Her echocardiogram showed severe pulmonary hypertension, mild mitral regurgitation, and an ejection fraction of 60% without regional wall motion abnormalities.

During her hospital course, she developed anemia, with her hemoglobin dropping from 9 g/dL on day six to 6.8 g/dL on day fifteen. She was then transfused with two packed red blood cell (pRBC) units. The anemia evaluation revealed low haptoglobin, elevated lactate dehydrogenase, and a negative Coombs test. Peripheral blood smears lacked schistocytes but indicated that the patient had chronic normocytic anemia with elevated polychromasia in circulating nucleated erythrocytes.

Her renal function deteriorated again on day 11 with creatinine rising gradually to 2.9 mg/dL. Urinalysis revealed 11-20 white blood cell (WBC) per high-power field, more than 100 RBC, and a protein level of over 300, with a urine protein-to-creatinine ratio of 1.45. Serologies and a kidney biopsy were requested due to concerns over glomerulonephritis. Anti-neutrophil cytoplasmic antibody, serum protein electrophoresis, serum-free light chains, cryoglobulins, Anti streptolysin O antibody, and *Legionella* urine antigen tests were negative. Her serum C3 and C4 complement levels were both low, likely due to liver failure.

A kidney biopsy was performed. The biopsy revealed a MPGN pattern of injury. Immunofluorescence showed granular capillary wall deposits of IgA, IgG, and IgM, as well as C1q, kappa light chain, and lambda light chain, which are characteristic of immune-complex mediated MPGN with polyclonal deposits. Additionally, IgG subtype immunofluorescence was performed to exclude a monotypic antibody process. By subtyping, IgG subclasses were polytypic: IgG1, IgG2, and IgG3 were positive, and IgG4 was negative. By electron microscopy, the mesangial and peripheral capillary wall deposits were reiterated, but these electron-dense deposits showed an unusual fibrillary substructure (Figure 1). The differential diagnosis for such an injury pattern included autoimmune diseases, atypical infections, and hematologic processes, such as cryoglobulinemia. There was no evidence of an underlying autoimmune diseases, paraproteinemia, or cryoglobulinemia after a comprehensive evaluation.

As all her autoimmune tests and monoclonal protein studies came back negative, it was suggested that she should undergo a thorough investigation into infectious etiology. A repeat workup with urine cultures, blood cultures, human immunodeficiency virus (HIV) testing, viral hepatitis panel, Histoplasma antibodies, Blastomyces antibodies, Bartonella antibodies, and PCR for Epstein-Barr virus



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Figure 1 Kidney Biopsy. A: Light microscopy sections show enlarged glomeruli with lobular accentuation of the capillary loops and both mesangial and endocapillary hypercellularity [periodic acid-Schiff (PAS), 400 ×]; B: Silver-negative, PAS-positive deposits are seen along the capillary loops, resulting in extensive capillary wall remodeling (Jones methenamine silver, 400 ×); C: These deposits show a full-house pattern, highlighting with all immunoglobulins and complement components on both standard and pronase immunofluorescence studies (IgG, 400 ×); D and E: On electron microscopy, numerous organized, electron-dense deposits with fibrillary substructure are seen within the mesangial and peripheral capillary loop walls [E: Electron microscopy (EM), 6000 ×], including focal areas with stacked parallel arrays are seen (D: EM, 50000 ×).

(EBV), Cytomegalovirus (CMV), Anaplasma, Methicillin-resistant *Staphylococcus aureus*, and streptococcal urine antigen were all negative. Her echocardiogram was negative for endocarditis. She had elevated Anaplasma antibody titers, IgG 1: 512. Infectious disease was consulted, and they advised starting doxycycline. She was started on doxycycline and was also started simultaneously on pulse steroids and prednisone taper as her kidney biopsy showed edema and inflammation in the renal parenchyma (Table 1).

But her kidney function continued to deteriorate. The patient was informed of the biopsy results and treatment options. She was not in need of dialysis immediately but informed her that she might need it if her renal function continued to worsen. With her other comorbidities, and after discussion, our patient decided to pursue comfort-only measures rather than aggressive treatment options and was discharged to home hospice.

DISCUSSION

Since the first reported case in Wisconsin in 1990, cases of HGA have steadily increased, rising from 348 cases in 2000 to 5655 cases in 2019 with a peak of 5762 cases in 2017. Anaplasmosis is commonly reported in the Upper Midwestern and Northeastern United States. However, only 88 case reports have been published thus far[1].

Tick bites are the most common mode of transmission for Anaplasmosis, mainly Ixodes ticks. The most common symptoms are fever, malaise, myalgias, headache, anorexia, and gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal pain, cough, and occasionally a rash[1,2]. HGA symptoms and presentation are typically nonspecific and may be difficult to distinguish from other infections. Therefore, a high index of suspicion must be maintained. Diseases transmitted by the same vector, such as Lyme disease, Ehrlichiosis, and Babesiosis, are included in the differential diagnosis of Anaplasmosis; however, other zoonoses and non-vector-borne diseases should also be considered. Non-tick-borne infections, such as viral exanthems (human herpesvirus 6, EBV, enterovirus, adenovirus, and parvovirus B 19), and bacterial infections, are still considered in the differential

diagnosis of anaplasmosis (Endocarditis, N. meningitides, N. gonorrhea, and secondary syphilis)[3,4]. Anaplasmosis is a clinical condition, however due to the nonspecific presentation, a broader workup to rule out other tick-borne diseases should be considered. Anaplasmosis causes mild anemia, thrombocytopenia, and leukopenia, as well as a mildly to moderately elevated liver function test[5]. A peripheral blood smear may show morulae within granulocytes, but this is not conclusive. The most conclusive tests are the indirect fluorescent antibody test and the polymerase chain reaction, which show a four-fold increase in IgG-specific antibodies and Anaplasma DNA in a whole blood sample, respectively[1].

Many complications of Anaplasmosis have been reported, which include end-organ damage such as acute kidney injury, rhabdomyolysis[2], multiorgan failure, non-traumatic splenic rupture, pancreatitis, secondary hemophagocytic lymphocytosis, and meningoencephalitis. Anaplasmosis has been linked to kidney disease, which is uncommon. In our case, the patient developed acute kidney injury due to MPGN from Anaplasmosis, which is very rare[6].

In this case, our patient was hospitalized with a diagnosis of community-acquired pneumonia and given antibiotics. During her hospitalization, she developed an acute kidney injury which we suspected was due to hepatorenal syndrome. Her kidney function initially improved with treatment, but it deteriorated again with a nephritic pattern of injury as evidenced by hematuria and proteinuria on urinalysis. In addition, her kidney biopsy revealed an unusual MPGN pattern of injury.

MPGN typically manifests in childhood, though it can manifest at any age. The clinical presentation and progression are extremely variable, ranging from benign to rapidly progressive. Thus, patients may exhibit asymptomatic, acute nephritic syndrome, nephrotic syndrome, or even rapidly progressive glomerulonephritis symptoms. In addition, the degree of kidney impairment varies based on the underlying lesions in the kidney, such that if a kidney biopsy reveals proliferative lesions, one is more likely to have a nephritic phenotype[3]; those with crescentic MPGN may present with rapidly progressive glomerulonephritis; and those with both repair and sclerosis are more likely to have a nephrotic phenotype. The MPGN pattern results from two underlying pathologies: (1) Immune complex-mediated; and (2) Complement-mediated. The immune-complex-mediated MPGN injury pattern is caused by circulating immunoglobulin or immune complexes, and etiologies include monoclonal gammopathy, autoimmune or rheumatologic disease, infection, or idiopathic[3]. This injury pattern is characterized by immune deposits that stain with either IgG or IgM predominance; typically complement staining is present, but not as strong as immunoglobulin staining. By contrast, complement-mediated MPGN—which encompasses C3 glomerulonephritis and dense deposit disease—typically will stain predominately with C3 and will typically have either genetic or acquired complement pathway alterations[3].

Monoclonal processes—such as proliferative glomerulonephritis with monoclonal deposits—can present with an MPGN pattern. However, unlike other immune-complex mediated MPGN, the immune complexes are monoclonal, not polyclonal, though an underlying B-cell/plasma cell clonal process is not always discovered or present[7]. In this case, immunofluorescence tests for both κ and λ light chains were positive, suggesting a polyclonal process. IgG subtype staining also showed polytypic distribution, further corroborating a polyclonal process[7,8]. Additionally, a normal $\kappa:\lambda$ ratio and negative serum protein electrophoresis test for monoclonal proteins eliminated the need for a hematologic or oncologic evaluation.

However, infectious causes remained to be identified for MPGN-pattern nephritic renal injury. We performed a thorough infectious workup that included a viral hepatitis panel, Ehrlichia, Bartonella, Blastomyces, Histoplasma, HIV-1 and HIV-2 antibodies and antigens such as p24 and HIV Ag/Ab ratio, Anaplasmosis, Mycoplasma IgM and IgG, ascitic fluid studies, anti-strep-O titers, severe acute respiratory syndrome coronavirus 2, EBV, and CMV. Except for the anaplasmosis antibody, serum IgG 1:512 (normal IgG 1:64), which is 8 times higher than normal, all results were negative. This demonstrates that in our case, anaplasmosis is the underlying cause of the MPGN pattern nephritic etiology. Infectious disease was consulted, and a 14-d course of twice-daily doxycycline was given. She did not require dialysis and was started on high-dose prednisone with stabilization of her creatinine between 3.0 to 3.5 mg/dL and blood urea nitrogen between 130 and 140 mg/dL without significant uremic symptoms. Although she had anasarca, she did not require supplemental oxygen at the time of discharge. To control metabolic acidosis, sodium bicarbonate was added, and sevelamer was used for hyperphosphatemia. However, due to her current medical conditions and poor prognosis, the patient opted for comfort care, and she ultimately passed away.

CONCLUSION

Tick-borne diseases are relatively common, but early detection is essential. Due to obstacles such as the absence of objective, measurable evidence for these symptoms, it is difficult to determine whether a patient's complex of symptoms is the result of tick-borne disease or another cause. Due to these obstacles, there is a greater chance of overlooking tick-borne diseases as an etiology, which can result in complications and poor outcomes. Even though we reached a conclusion in our case and decided to initiate treatment, our patient had transitioned to comfort care measures only and declined further

treatment. Due to the increasing prevalence of renal involvement and other complications in tick-borne diseases, it is crucial to diagnose and treat tick-borne diseases in their earliest and most prevalent stages.

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Moderate stepwise restriction of potassium intake to reduce risk of hyperkalemia in chronic kidney disease: A literature review

Ali AlSahow

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Abstract

A potassium-rich diet has several cardiovascular and renal health benefits; however, it is not recommended for patients with advanced chronic kidney disease or end-stage kidney disease because of the risk of life-threatening hyperkalemia. To assess the strength of evidence supporting potassium intake restriction in chronic kidney disease, the medical literature was searched looking for the current recommended approach and for evidence in support for such an approach. There is a lack of strong evidence supporting intense restriction of dietary potassium intake. There are several ways to reduce potassium intake without depriving the patient from fruits and vegetables, such as identifying hidden sources of potassium (processed food and preservatives) and soaking or boiling food to remove potassium. An individualized and gradual reduction of dietary potassium intake in people at risk of hyperkalemia is recommended. The current potassium dietary advice in chronic kidney disease needs to be reevaluated, individualized, and gradually introduced.

Key Words: Chronic kidney disease; Potassium intake; Plant-based diet; Hyperkalemia; Potassium removal

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Core Tip: A potassium-rich diet has several cardiovascular and renal health benefits; however, it is not recommended for patients with advanced chronic kidney disease or end-stage kidney disease because of the risk of life-threatening hyperkalemia. However, there is a lack of strong evidence supporting this restrictive approach. There are several ways to reduce potassium intake without depriving the patient of fruits and vegetables, such as identifying hidden sources of potassium (processed food and preservatives) and soaking or boiling food to remove potassium. An individualized and gradual reduction of dietary potassium intake in people at risk of hyperkalemia is recommended.

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INTRODUCTION

A potassium-rich diet has several cardiovascular and renal health benefits[1-4]. However, it is not recommended in patients with advanced chronic kidney disease (CKD) or end-stage kidney disease (ESKD) because of the risk of hyperkalemia[5]. In fact, restriction of dietary potassium intake is the current standard of care. Due to the lack of strong evidence supporting this approach, there are calls to reevaluate and individualize the potassium dietary advice for patients with CKD[1,2]. In this review, the current recommendations, the argument against a restrictive approach, and an individualized, gradual reduction of dietary potassium intake were discussed.

Potassium intake and health

A potassium-rich diet can help decrease blood pressure and the risk of CKD and its progression, cardiovascular disease, stroke, and mortality[1-4]. Fruits and vegetables in most diets supply the majority of dietary potassium[5]. The alkaline content of such a potassium-rich, plant-based diet may correct CKD-associated metabolic acidosis. Fiber from potassium-rich fruits and vegetables improves the lipid profile, lowers body weight, increases stool volume and frequency, improves colonic epithelium integrity reducing toxin absorption, and improves the gut microbiome reducing systemic inflammation[1-4]. The Kidney Disease Outcomes Quality Initiative 2020 nutrition guideline suggested increasing fruit and vegetable intake to help reduce weight, blood pressure, and net acid production, all of which may help lower the rate of CKD progression[6]. A plant-based diet also helps decrease the risk of calcium oxalate stone formation by increasing urinary citrate levels and reducing the calcium excretion rate[3].

The minimum daily requirement for potassium in adults, estimated based on its unavoidable loss through sweat, stool, urine, and other sources, is about 1.6 g[7]. **Table 1** Lists the recommended daily intake of potassium for the general population. It is important to know that the majority of people around the world consume less than what is recommended[8-10].

Dietary potassium intake recommendations in adult patients with CKD

Patients with an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m² are generally at low risk of hyperkalemia when consuming the recommended amount of potassium for the general population, even during treatment with renin angiotensin aldosterone system (RAAS) blockers. Hyperkalemia may develop in patients receiving a high dose of RAAS blockers and/or who have a high potassium intake (> 5 g/d) in the presence of severe heart failure and/or diabetes[8]. **Table 2** outlines the current potassium intake recommendations for patients with advanced CKD (stages 3b-5) and ESKD to avoid hyperkalemia. It reveals a lack of consensus regarding recommendations for a low potassium diet. A low potassium diet is defined as a dietary intake of 2-3g/d of potassium[5]. In CKD populations, potassium intake is estimated to average around 2.4 g/d[11].

Uncertainties and challenges of dietary potassium restriction in CKD

Recommendations to limit potassium intake in CKD and ESKD are standard practice for two reasons: to prevent acute hyperkalemia (when postprandial potassium absorption exceeds cellular uptake and body excretion); and to prevent chronic hyperkalemia (when potassium bioaccumulation or total body potassium exceeds cellular uptake and potassium excretion)[12]. However, this approach also restricts intake of fruits, vegetables, dairy, grains, nuts, and legumes because they are major sources of potassium[5,12-14]. This in turn deprives patients of the health benefits discussed earlier, and it may need to be reevaluated for several reasons.

There is a lack of direct evidence regarding the benefit of restricting potassium intake in CKD from randomized controlled trials[15,16]. The results from observational studies regarding the association between higher urinary potassium excretion and mortality and kidney outcomes are conflicting[4,6,15]. Dietary potassium restriction is difficult because it requires lifestyle changes that may lead to loss of enjoyment in food and impact social activities. It may result in extra financial costs for special diets[15,16]. Restriction may lower the intake of other beneficial nutrients resulting in a poor diet, which may contribute to malnutrition in advanced CKD[17] and may lead to cardiovascular disease[18].

The National Kidney Foundation defines potassium-rich food as food with more than 200 mg of potassium per serving [19]. This arbitrary threshold can be confusing. For example, tangerines are a low-potassium food while oranges are a high-potassium food, despite having relatively similar nutrient contents and densities[20]. In addition, evidence suggests that gut-kidney kaliuretic signaling initiates urinary potassium excretion before the rise in plasma potassium and independent of plasma potassium and plasma aldosterone[4], which may explain why little to no association exists between serum potassium levels and potassium intake in CKD patients[16,21-24].

An unprocessed plant-based diet rich in potassium may not always lead to hyperkalemia for several reasons. Not all fruits and vegetables are rich in potassium[1]. The 24-h urine potassium recovery from animal-based diets is about 80% and from unprocessed plant-based diets is about 50%-60%. This lower bioavailability of unprocessed plant potassium might enable CKD patients to benefit from plant-based diets without precipitating hyperkalemia[1,3,25]. Plants are the

Table 1 Recommended adequate intake of potassium for adults in the general population

Institution	K intake g/d
WHO and EFSA[32,33]	3.5
United States and Canada[34,35]	
Male	3.4
Female	2.6
Japan[7]	2.7–3.0

EFSA: European Food Safety Authority; K: Potassium; WHO: World Health Organization.

only natural source of fiber, a nondigestible, nonabsorbable carbohydrate polymer that increases stool quantity and frequency, facilitating colonic elimination of potassium and protecting against hyperkalemia[3]. Plants provide a natural alkali, which may facilitate the transfer of potassium to the intracellular compartment, especially in metabolic acidosis[1, 3,5,16]. Complex carbohydrates found in fruits and vegetables increase the insulin-mediated cellular uptake of potassium, helping to lower the risk of hyperkalemia[1,3,16]. The mineral content of vegetables varies with vegetable size, weather conditions, and cultivation techniques[26]. Many dietary recommendations are based on the mineral content of raw whole foods and not chopped, cooked foods[23,27]. Restricting sodium intake and encouraging a potassium-rich, plant-based diet may help control hypertension, reducing the need for hyperkalemia-inducing antihypertensive medications, such as β -blockers. It may also allow the reduction of the dosage of RAAS blockers[2], although this approach is controversial due to the negative effects on kidney and patient survival[17,15].

Potassium restriction should also be reevaluated because guidelines do not make specific recommendations for potassium in processed food or food additives and do not discuss potassium bioavailability. Potassium additives provide almost three times the amount of potassium found in additive-free counterparts, and potassium additives in processed foods have a high bioavailability contributing to hyperkalemia[24]. Because of the pressure on the food industry to decrease sodium in processed food, but not the salty taste, potassium use has increased in low-sodium processed foods [24,28,29]. Advice to restrict sodium alone for patients who need dietary sodium and potassium restriction may inadvertently increase potassium intake if a patient unknowingly switches to low-sodium products with potassium additives[30]. Moreover, advising CKD patients to restrict potassium-rich food without proper counseling may lead them to choose sodium- and potassium-rich processed foods over healthier alternatives[30]. Potassium-based food additives are found in precooked or shelf-stable foods, powdered dressings, sauces, preserved meats, stuffed pasta, jellies, concentrated fruit juices, processed cheeses, and margarine[5]. A list of potassium-based food additives is available elsewhere [31].

There are pitfalls associated with the tools used to estimate dietary intake of potassium. Plasma potassium levels are usually measured before hemodialysis and in a fasting state for non-hemodialysis (not a postprandial state). This timing is better suited to evaluate chronic hyperkalemia risk but not to detect acute postprandial hyperkalemia[30]. The standard assessment method is a 24-h urine collection, which assumes that 24-h urinary potassium excretion always reflects 70% of ingested potassium. However, collection errors may lead to incorrect assumptions and advice[28]. In addition, a single collection cannot accurately estimate potassium intake due to day-to-day variability in intake, gastrointestinal excretion, which is higher at low eGFR, and cell distribution. Spot urine should not be used to estimate intake at an individual level [11,15].

Non-urinary-based dietary assessment tools (food frequency questionnaires, diet records, and 24-h diet recalls) are not affected by changes in potassium homeostasis in CKD but rely on food databases. Thus, database inaccuracies (*e.g.*, differences in nutrients between processed, restaurant-cooked, and home-cooked foods) can lead to measurement errors [11,15].

Food frequency questionnaires record the consumption frequency of a predefined list of foods and beverages over weeks or months. It is the most cost-effective and time-saving method with a low burden, but errors occur due to recall bias (*i.e.*, respondents not correctly memorizing intake) and when questionnaires are not relevant to local dietary habits or seasonal changes. Furthermore, they may not account for potassium additives and substitutes and cooking methods[11, 15].

Diet recall documents all foods and beverages consumed in the previous 1-7 d with moderate precision, cost, time, and burden. However, the method is prone to recall bias and underreporting, especially in overweight individuals. Precision is acceptable because quantities of consumed foods are defined, including potassium additives and cooking methods. However, more detailed intake information increases data collection complexity[11,15].

Diet records are prospective documentation of intake with minimal recall bias, and it is the most accurate if foods are documented and weighed correctly. However, it is costly and time consuming. Respondents may simplify or underreport complicated meals or even alter eating behaviors choosing healthier foods (selective reporting). Keeping records for more than 4 d may lead to inaccurate results due to respondent fatigue. It is also less suitable for CKD patients, in whom limited health literacy and cognitive impairment are common[11,15].

A gradual, individualized approach

A stepwise reduction in potassium intake is advised to ensure a balanced intake of fresh fruits and vegetables and fiber

Table 2 Recommended potassium intake for adult patients with chronic kidney disease

Source	Advice
KDOQI	
2000[36]	CKD 1-5 ND: Unrestricted intake unless serum potassium level is elevated; HD: Intake up to 2.7-3.1 g/d; PD: Intake close to 3-4 g/d
2004[18]	CKD 1-2: intake > 4 g/d; CKD 3-4: intake 2-4 g/d
2020[6]; with the Academy of Nutrition and Dietetics	Statement 3.3.2: in adults with CKD 1-4, we suggest that prescribing increased fruit and vegetable intake may decrease body weight, blood pressure, and net acid production (2C); Statement 6.1.1: in adults with CKD 1-4, we suggest reducing net acid production through increased dietary intake of fruits and vegetables (2C) to reduce the rate of decline of residual kidney function; Statement 6.4: Adjust dietary potassium intake to maintain serum potassium within the normal range for adults with CKD 3-5D (opinion)
2019[19]; NKF educational website	A potassium restricted diet is typically about 2 g/d. A physician or dietitian will advise patient on the specific level of restriction needed based on individual health
EBPG	
2007[37]	Recommendation of 4.2 g/d; in patients with pre-dialysis serum potassium greater than 6 mmol/L, a daily intake of potassium of 1950-2730 mg or 1 mmol/kg IBW is recommended
Spanish Society of Nephrology	
2008[38]	A low-potassium diet (1.5-2.0 g/d) is recommended for GFR < 20 mL/min or GFR < 50 mL/min if potassium-increasing drugs are taken
Academy of Nutrition and Dietetics	
2010[39]	Daily potassium intake of less than 2.4 g for CKD stages 3-5 who exhibit hyperkalemia
2014[40]	CKD stages 3-5 not on dialysis: no restriction until hyperkalemia is present, then individualized; HD: 2-4 g/d or 40 mg/kg of BW/d; PD: individualized to achieve normal serum levels
Australian guidelines	
2005[41]	Reduced potassium diet should commence when serum potassium in pre-dialysis patients is > 5.5 mmol/L (Opinion). A reduced potassium diet limits the 24-h intake to about 3.1 mg
2013[42]	Early CKD patients with persistent hyperkalemia restrict their dietary potassium intake with the assistance of an appropriately qualified dietitian (2D)
Italian Society of Nephrology	
2019[43]	Statement 1.2: serum potassium $\geq$ 5 mmol/L must be considered pathologic in CKD; Statement 1.3: restriction of potassium intake for non-dialysis CKD of mild-to-moderate degree is not recommended unless potassium levels are above 5 mmol/L in the absence of any other apparent cause. Then, it is recommended to limit food with high potassium content, especially if low in fiber, and pretreat (soaking and boiling) before cooking to remove potassium; Statement 2.3: restrict potassium intake to 2-3 g/d for advanced CKD and HD patients
Renal Association	
2020[17]	A low potassium diet should be instituted for patients with advanced CKD and ESKD with persistent hyperkalemia with serum potassium > 5.5 mmol/L; a low potassium diet is defined by a dietary intake of 2-3 g/d
Cupisti <i>et al</i> [5]	Limit intake to 2.5-3.0 g/d or 1 mmol/kg/IBW for mild hyperkalemia of 5.0-5.5 mmol/L; limit intake to 2.0-2.5 g/d for moderate hyperkalemia of 5.5-6.0 mmol/L; 1.5-2.0 g/d for severe hyperkalemia of 6.0-6.5 mmol/L
Yamada <i>et al</i> [7]	Limit intake to $\leq$ 2 g/d for eGFR $\geq$ 30 and $\leq$ 1.5 g/d for eGFR < 30; limit intake to $\leq$ 2 g/d for HD and 2.0-2.5 g/d for PD
Kalantar-Zadeh <i>et al</i> [44]	Recommended potassium intake is the same as for the general population: (1) eGFR $\geq$ 60 mL/minute/1.73 m ² without substantial proteinuria (< 0.3 g of protein/d) but high risk for CKD because of DM, HTN, PCKD, or a solitary kidney, <i>etc</i> ; or (2) eGFR of 30-59 mL/minute/1.73 m ² without substantial proteinuria (unless frequent or severe hyperkalemia episodes are likely); Limit potassium intake to < 3 g/d: (1) eGFR < 30 mL/minute/1.73 m ² if hyperkalemia occurs frequently during high-fiber intake; (2) Any eGFR if there is substantial proteinuria and frequent hyperkalemia during high-fiber intake; (3) Patients with good residual kidney function transitioning to dialysis if hyperkalemia occurs frequently during high-fiber intake; or (4) Dialysis patients or patients at any stage with existing or imminent protein-energy wasting defined according to the International Society of Renal Nutrition and Metabolism criteria
Clegg <i>et al</i> [13]	Limit potassium intake to 3 g/d

BW: Body weight; CKD: Chronic kidney disease; DM: Diabetes mellitus; EBPG: European Best Practice Guidelines; eGFR: Estimated glomerular filtration rate; ESKD: End-stage kidney disease; GFR: Glomerular filtration rate; HD: Hemodialysis; HTN: Hypertension; IBW: Ideal body weight; KDOQI: Kidney Disease Outcomes Quality Initiative; ND: Not on dialysis; NKF: National Kidney Foundation; PCKD: Polycystic kidney disease; PD: Peritoneal dialysis.

Table 3 Strategies to reduce the risk of hyperkalemia in chronic kidney disease before employing potassium dietary restriction

Strategy
Calculate the eGFR to assess the patient's risk of hyperkalemia
Avoid hidden sources, especially potassium-based additives in processed food and salt substitutes in low-sodium processed food
Increase stool frequency to increase the proportion of potassium excreted by the gut
Identify and correct non-dietary factors that influence serum potassium levels to keep potassium within normal range: (1) Drugs that may elevate serum potassium that can and should be discontinued/avoided (NSAIDs, COX-2 inhibitors, PPIs, potassium supplements, herbal remedies); (2) Inorganic metabolic acidosis associated with advanced CKD when serum bicarbonate level < 22 mmol/L; (3) Uncontrolled DM. Insulin deficit and/or hyperglycemic hyperosmolality lower acute potassium load movement into cells; and (4) Other causes that may directly or indirectly increase potassium level include volume depletion, adrenal insufficiency, catabolic state (major cell damage, hemolysis) and GI problems (diarrhea, constipation, bleeding)
Reduce the dose of medications known to elevate serum potassium level if in use or switch to an alternative if possible: RAASi (DRA, ACEI, ARB, MRA, ARNI, ASI), β -Blockers, potassium-sparing diuretics (Amiloride, Triamterene), calcineurin inhibitors (cyclosporine, tacrolimus), digoxin, heparin, trimethoprim/co-trimoxazole
Use diuretics. The effect depends on eGFR. Dialysis patients with reasonable residual kidney function may respond to loop diuretics. Diuretics work best when diuresis is desired, or an additional antihypertensive agent is considered
Implement sick-day rules by advising patients on the risk of AKI and hyperkalemia during acute illness and on measures to avoid them. However, it can be difficult and counterproductive
Improve potassium removal in hemodialysis (thrice weekly, 4-h sessions), which is mainly by diffusion: (1) Increase session duration and frequency, increase blood and dialysate flow, increase filter surface area, correct vascular access status recirculation, and use lower dialysate potassium; (2) Higher dialysate glucose concentration triggers insulin release, which enhances cellular uptake of potassium; (3) Higher bicarbonate bath concentration increases blood pH, which enhances cellular uptake of potassium; (4) Minimize pre-dialysis exposure to drugs that increase cellular uptake of potassium such as insulin and β_2 -agonist inhalers because they reduce pre-dialysis potassium, which reduces dialytic removal and exacerbates potassium rebound post-dialysis
Use one of the newer generation potassium binders (patiomer or sodium zirconium cyclosilicate). However, they primarily target chronic hyperkalemia not acute postprandial hyperkalemia and may increase pill burden

Information compiled from references[1,3,5,13,15-17,45-51]. ACEI: Angiotensin converting enzyme inhibitor; AKI: Acute kidney injury ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor/neprilysin inhibitor; ASI: Aldosterone synthase inhibitor; CKD: Chronic kidney disease; COX-2: Cyclooxygenase 2; DM: Diabetes mellitus; DRA: Direct renin antagonist; eGFR: Estimated glomerular filtration rate; GI: Gastrointestinal; MRA: Mineralocorticoid receptor antagonist; NSAID: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; RAASi: Renin angiotensin aldosterone system inhibitors.

Table 4 Strategies to gradually introduce a mild potassium-restrictive dietary plan

Strategy	Steps
Ensure care is patient centered	(1) Involve dietitians, nurses, psychologists, pharmacists, and social workers if resources allow to ensure patient understanding. Clarify roles and responsibilities of each regarding dietary education to reduce conflicting information and deliver nutrition training to non-dietetic staff to promote consistency of message; (2) Individualize the plan according to patient's lifestyle, and personal, religious, and sociocultural background. Train staff, particularly dietitians, to ensure expertise on culturally important foods and dietary patterns; (3) Explain the plan's benefits and limitations and give the patient ample time to accept, to change dietary habits, and to adhere. Plant-based diets can be eco-friendly and economically advantageous. These arguments may promote adherence; (4) Adapt to all levels of education. Health literacy improves patient access and use of health information. Many patients have low health literacy, which may hinder communication, comprehension, and use of digital technology, prolonging the time to convey the message; (5) Identify vulnerable patients (young, socially isolated) who may need more nutritional education and support; and (6) Provide early and continuous access to the renal dietitian for collaboration on plan design and implementation
Instruct patients to identify potassium content of foods to avoid potassium-rich food. Food with > 200 mg of potassium/serving is defined as a potassium-rich food by the National Kidney Foundation	(1) Check serving size/weight. A large low-potassium food serving may have more potassium than a small high-potassium food serving; (2) Spread potassium-rich food items throughout the day to avoid acute postprandial hyperkalemia; (3) Increase the intake of low-potassium to fiber ratio fruits (apple, apricot, berries) and vegetables (green beans, peas, asparagus, lettuce, onions) and reduce the intake of high-potassium to fiber ratio food (processed juice and sauces); (4) Avoid food items that are very rich in potassium, such as edamame, molasses, and white and black beans; (5) Switch to soy-, rice-, and almond-based milk and yogurt because they may have less potassium and phosphorus than dairy; and (6) Avoid 93% lean ground beef since it has substantially more protein, phosphorus, and potassium than 70% lean ground beef
Describe food preparation methods and cooking procedures that may help reduce the potassium content of food	See Table 5
Apply dietary plan to real life	(1) Invite and engage both patients and family members responsible for buying and preparing food (spouse, relative) in the appointments with the dietitian to translate dietary recommendations into accessible plans; (2) Adopt a stepwise approach allowing patients to adapt to dietary recommendations gradually. Patients do not eat calories, protein, or carbohydrates; they eat food, therefore, translate information about nutrients into food using food models, pictures, and recipes to make dietary counseling real and achievable; (3) Simplify nutrition

education/advice particularly for those with multiple dietary needs. Avoid weighing or counting servings if possible so it is more practical for most patients. Use the hand to estimate serving size; (4) Explore unrestricted food. Discussion should focus less on what is not allowed and more about what is. Counseling based on food habits highlights foods that should be avoided with alternatives for replacement. For example, animal-based food (cow's milk) may be replaced by plant-based food (vegetable milk such as soy, almond, and coconut); (5) Nothing should be "forever." Social life is shared around a table; more restaurants have plant-based options, but the main courses in family meetings are often animal-based. Patients will not easily give up food they love. Allowing occasional freedom can improve long-term adherence; (6) Suggest cooking classes for recipes desired by patients to stimulate emotional involvement. Explore seasonal fruits and vegetables; (7) Offer positive feedback for the patient/caregiver during visits to motivate the patient to continue with the plan. Show how it affects laboratory values, intradialytic weight over time, or even number of pills patient is taking; (8) Meal delivery service may benefit patients who live alone or have difficulty shopping and preparing meals; and (9) Utilize the internet and social media: (a) Smartphones and tablets help interactive sessions (sharing pictures of dishes, describing sizes and preparation methods); (b) Telehealth/virtual nutrition counseling supports patients who need frequent reinforcement that outpatient clinic timing does not allow for or for those who have difficulty attending in-person clinical settings. They are cost effective in communities where long distances represent a barrier to face-to-face nutritional education; (c) Dietitian-facilitated and -supervised online peer support programs can promote healthful dietary behaviors. Age and cultural appropriateness of group participants should be considered; and (d) Online resources and technology-based interventions using smart phones (E-learning) can be used as platform for teaching and workshops reinforcing nutrition education and self-management plans

Information compiled from references[1,2,5,12,15,16,19,20,31,45-50,52].

Table 5 Food preparation methods to help lower food contents of potassium and ease restriction intensity

Strategy	Tips
Wash and peel the fruit and vegetable skin to lower potassium content then chop into small pieces. Peeling reduces fiber content	
Place in cold water so they do not darken, then rinse in warm water for a few seconds	
Soak for at least 4 h in warm water, then rinse, change the water, and soak for another 12 h (longer for legumes)	(1) Use ten times the amount of water to the amount of fruits or vegetables; (2) Water may need to be changed every 4 h for potassium-rich items; (3) Legumes may need to be soaked for 36 h at a ratio of 100 g per 1.5 L water with frequent changing of water; (4) Soaking lowers potassium more efficiently in water-rich soft foods like tomatoes and apples compared to potatoes or chocolate; (5) Soaking fresh potatoes, canned potatoes, and frozen fries alone without cooking afterward is ineffective in removing potassium; (6) Soaking alone is also ineffective for potassium removal from bananas, but boiling improves its removal; and (7) Soaking after normal cooking may increase potassium removal
Rinse afterwards under warm water for a few seconds before eating or cooking	
Cook vegetables with five times as much water as vegetables	(1) Vegetables can be boiled in conventional cookware, a pressure cookware/autoclave, or microwave oven; (2) Potassium-rich items may need to be boiled twice. The double cooking technique; (3) Potassium removal by cooking shredded potatoes exceeds that of cooking cubed potatoes; (4) Adequate soaking followed by cooking may allow legume consumption twice weekly. Soaking dried legumes alone is ineffective for potassium removal; cooking after soaking significantly reduces potassium content. Cook in water at a ratio of 100 g per 1.5 L water (3 L water for dried chickpeas due to the long cooking duration they need). Canned legumes, drained and rinsed, contain less potassium and phosphorus than dried legumes, and the final contents after soaking and normal cooking make them a better alternative to the laborious preparation method for dried legumes. However, precooked legumes often contain salt and/or salt substitutes; (5) Freezing of green beans/chard (home frozen and industrial frozen) alone does not reduce potassium content. However, it leads to greater reduction of potassium contents when followed by soaking than soaking fresh ones. Cooking without soaking reduces potassium content less than cooking of soaked frozen ones. Soaking plus cooking is superior to either soaking alone or cooking without soaking alone for fresh green beans / chard; (6) Cooking methods that avoid contact with water (dry heat cooking, steam cooking, dehydration cooking) remove less potassium; and (7) Aromatic herbs can improve food taste and palatability reduced by peeling and boiling

Information compiled from references[6,19,20,52-60].

by patients with advanced CKD who are not prone to hyperkalemia[5,16]. Table 3 summarizes several strategies that should be implemented to minimize the risk of hyperkalemia before restricting potassium intake. Table 4 describes the steps to gradually restrict potassium intake and to minimize the impact of this approach on the patient. Table 5 describes cooking methods that can help reduce potassium levels in fruits and vegetables to increase the number of permissible food items.

CONCLUSION

Although potassium intake restriction is the standard of care in advanced CKD and ESKD, there is a need for the reevaluation of this approach in CKD patients who do not have hyperkalemia. There are health benefits of a plant-based, potassium-rich diet, and it is difficult to implement a low-potassium diet. There is scarce and inconsistent data attributed to dietary potassium in patients with CKD, and the risk of hyperkalemia may have been overstated. Under the supervision of a skilled dietician, the list of permissible food items may be gradually expanded by introducing unprocessed and properly prepared plant-based foods, especially those with a low potassium to fiber ratio, to improve the quality of food intake. Further research on moderate gradual liberalization of potassium intake in patients with CKD is certainly warranted.

FOOTNOTES

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Immunoglobulin A vasculitis nephritis: Current understanding of pathogenesis and treatment

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Abstract

The clinical spectrum of immunoglobulin A vasculitis nephritis (IgAVN) ranges from the relatively common transitory microscopic hematuria and/or low-grade proteinuria to nephritic or nephrotic syndrome, rapidly progressive glomerulonephritis, or even renal failure. Clinical and experimental studies have shown a multifactor pathogenesis: Infection triggers, impaired glycosylation of IgA1, complement activation, Toll-like-receptor activation and B cell proliferation. This knowledge can identify IgAVN patients at a greater risk for adverse outcome and increase the evidence for treatment recommendations.

Key Words: Immunoglobulin A vasculitis nephritis; Immunoglobulin A vasculitis; Henoch-Schoenlein purpura; Immunoglobulin A nephropathy; Vasculitis, glomerulonephritis

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Core Tip: This review summarizes the main mechanisms involved in the pathogenesis of immunoglobulin A vasculitis nephritis and the recent treatment development, in order to decrease the risk of kidney disease progression.

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INTRODUCTION

Immunoglobulin A (IgA) vasculitis (IgAV), also known as Henoch-Schoenlein purpura (HSP), is the most common systemic vasculitis in children. It is defined by the presence of non-thrombocytopenic palpable purpura or petechiae (mandatory criterion) predominantly located in the lower limbs, plus abdominal pain or IgA deposition in tissue biopsy or arthritis/arthralgia or renal disease[1,2]. 20%-80% of patients with IgAV develop renal involvement, termed IgAV nephritis (IgAVN), which is the key element in affecting long-term outcome[3-5].

According to the European SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) plane[6], all IgAV patients should be investigated for renal involvement at diagnosis and throughout follow-up by measuring blood pressure, determining the presence of haematuria, quantifying albuminuria and/or proteinuria and, finally, estimating glomerular filtration rate (eGFR)[7]. If initial tests are normal, they need to be monitored for at least 6-12 mo[8-12]. The renal biopsy should be performed in the case of impaired eGFR, persistent proteinuria, nephrotic (*e.g.*, severe proteinuria, low serum albumin levels and oedema) or nephritic (*e.g.*, impaired eGFR, hypertension, haematuria/proteinuria) syndrome.

This review summarizes some important current aspects of IgAVN and most importantly the understanding of its pathogenesis and treatment founded on the results of a multitude of clinical and experimental researches.

IGA NEPHROPATHY AND IGAVN

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in children and adults. Exclusive renal involvement is characterized by a very slow progression, typical of chronic diseases[9]. In contrast, IgAVN is the most common cause of secondary glomerulonephritis in pediatric age; renal involvement tends to have an acute and self-limiting course similar to that of post-infectious glomerulonephritis, but if persistent it can lead to chronic kidney disease and end-stage renal disease approximately 20 years after diagnosis[10,11].

In a retrospective study based on the epidemiological, clinical and laboratory characteristics of IgAV patients, Carucci *et al*[12] investigated the initial risk factors for IgAVN development, suggesting that age at diagnosis and abdominal pain were associated with a higher risk of onset of the kidney disease in pediatric age. However, additional long-term studies are still needed for the retrospective study type[12].

According to a Japanese study conducted by Komatsu *et al*[13], IgAVN has two peaks in incidence (1-19 years and 60-69 years), while IgAN has an isolated peak in incidence during the 4th decade. Compared to IgAN, IgAVN is clinically more severe (especially considering the parameters of proteinuria and hypoalbuminemia), and histologically more aggressive, with a higher percentage of proliferative endocapillary glomerulonephritis and crescentic glomerulonephritis [13].

Despite these differences, several studies have shown that the two diseases share the same pathogenesis, namely a defect in IgA1 glycosylation[14-16]. In addition, glomerular histologic findings can be identical, ranging from focal proliferative lesions with diffuse mesangial IgA deposits to extracapillary proliferative lesions with crescent formation, making it sometimes impossible to distinguish IgAN from IgAVN in the absence of extrarenal signs. For this reason, the two entities have recently been considered to be two different manifestations of the same pathology and in 2012, during the Chapel Hill Consensus Conference on the nomenclature of vasculitis, it was decided to replace the definition "HSP" with that of "IgAV", considering it the systemic form of IgAN[17,18].

In an interesting case series by Kamei *et al*[10], 11% of patients with an initial diagnosis of IgAN subsequently (over a period ranging from 5 mo to 14 years) developed palpable purpura, which allowed the diagnosis to be changed to IgAVN, supporting the hypothesis that IgAN and IgAVN are actually two variants of the same disease. In almost all of these patients, worsening of nephritis was described after the onset of purpura[10]. For this reason, patients diagnosed with IgAN require careful and prolonged follow-up with special attention to the possible appearance of purpura, a sometimes nuanced finding that therefore risks going unnoticed[19].

PATHOGENESIS

IgAVN shares many pathophysiological features with IgAN (Table 1). The aim of this review is to update the pathogenesis of IgAVN by providing more information regarding impaired glycosylation of IgA1, generation of immune complexes and their kidney deposition, and finally concerning complement activation and stimulation of the mesangial cells, which leads to their expansion and cytokine release[20]. Toll-like-receptor (TLR) activation and B cell proliferation, infection triggers, and genetic factors are also involved in the IgAVN pathogenesis[21].

Infection triggers

Helicobacter pylori[22], *Streptococcus pneumoniae* and *Haemophilus Influenzae*[23,24] are the main pathogens associated with the disease. Infections may be involved in the pathogenesis of IgAVN through two mechanisms. The first is due to the presence of N-acetylgalactosamine (GaINAc) on the superficial side of pathogens stimulating the output of cross-reactive IgA and IgG that identify galactose-deficient IgA1 (Gd-IgA1). Alternatively, microbial agents containing antigens similar to structures on the vessel wall generate a cross-reactive autoantibody response[25].

Table 1 Mechanism of immunoglobulin A vasculitis nephritis pathogenesis

No.	Mechanism of IgAVN pathogenesis
1	Infection triggers (<i>Helicobacter pylori</i> , <i>Streptococcus pneumoniae</i> and <i>Haemophilus Influenzae</i>)[22-25]
2	Genetic factors[26-28]
3	Impaired glycosylation of IgA1 (Gd-IgA1)[29-41]
4	Complement activation[42-45]
5	TLR activation and B cell proliferation[46-48]
6	AECAs[49-51]
7	NAP1r[52,53]
8	Elevated plasma levels of IgE, eosinophil activation, higher levels of ECP and renal α -SMA[54-56]

IgAVN: Immunoglobulin A vasculitis nephritis; Gd-IgA1: Galactose-deficient-immunoglobulin A; TLR: Toll-like-receptor; AECAs: Anti-endothelial cell antibodies; NAP1r: Nephritis-associated plasmin receptor; α -SMA: α -smooth muscle; ECP: Eosinophil cationic protein.

Genetic factors

Little is known yet about the role of genetic factors in the IgAVN pathogenesis, although the presence of ethnic and geographical differences in the incidence of IgAV and IgAVN would indicate its involvement[26,27]. Furthermore, several genes involved in cytokine and chemokine production, complement activation, and regulation of endothelium activity have been implicated in IgAV susceptibility[25,28].

Serum levels of Gd-IgA1 are heritable in both IgAN and IgAVN, indicating that the genetic predisposition to develop IgAVN and IgAN is the same[16].

Impaired glycosylation of IgA1

IgAVN and IgAN appear to have identical pathophysiology, with only quantitative differences[29]. High levels of IgA and IgA-containing immune complexes have been observed in both cases. However, this serum abnormality is not a sensitive marker for diagnosis[30]. IgA1, not IgA2, is the main component of IgAN and IgAVN. The IgA1 molecule has a hinge region which contains up to six O-linked glycan chains made up of GalNAc, typically with β 1,3-linked galactose (Gal) attached to it[31,32]. Normally, mono- and di-sialylated Gal-GalNAc disaccharides are present in healthy subjects[33,34]. Elevated levels of Gd-IgA1 have been detected in patients with IgAVN and IgAN, compared with the healthy population and patients with other glomerular diseases[35]. Therefore, Gd-IgA1 now plays a pivotal role in both IgAN and IgAVN pathogenesis[36].

It has been reported that these patients have decreased galactosylation of O-glycans, resulting in reduced β 1,3-galactosyltransferase activity in the peripheral B cells of patients. Reduced β 1,3-galactosyltransferase activity leads to a lack of terminal β 1,3-galactosyl residues in the hinge region of IgA1[15,37].

Gd-IgA1 polymer molecules are known to be anti-glycan IgA1 or IgG, resulting in the formation of circulating immune complexes that are deposited in the renal mesangium and subepithelial and subendothelial space, and which incite glomerular injury. In IgAVN, IgA deposit can be found not just in the kidney, but also in other sides like the skin, and larger immune complexes are found compared to IgAN[15]. Deposition of IgA1-containing immune complexes appears to be mediated by a relationship with mesangial transferrin 1 (CD71) and CD89 receptors, also known as Fc α RI, which may occur as a transmembrane receptor in myeloid cells. These receptors on the mesangial surface are more highly expressed than in healthy children.

The monomeric IgA can bind, but without crossbinding with Fc α RI, leading to anti-inflammatory reactions[38]. Monovalent Fc α RI targeting results in the formation of intracellular structures called "inhibisomes", which obstruct the signaling of nearby activated receptors. This process is referred to as ITAM inhibitory signaling (ITAMi) and results in a downregulation of immune activation. In contrast, IgA immune complexes binding to Fc α RI on neutrophils induce activating ITAM signaling, resulting in multiple pro-inflammatory functions. In addition, the activation of Fc α RI induces the LTB₄ chemoattractant release, resulting in neutrophil migration[39,40].

Consequently, after deposition the mesangial cells start to proliferate and produce other components of the extracellular matrix, and also inflammatory and profibrogenic cells such as cytokines and chemokines[35-41].

Complement activation

The activation of the complement system plays an important role in the pathophysiology of IgAV and IgAVN, including infection triggers and genetics. Indeed, mesangial deposits contain the complement components C3 and C5-C9, which are able to form the attack complex that destroys the membrane of target cells[42]. High levels of C3a, C5a and Bb have also been documented in the serum of pediatric patients with acute IgAV. C5a is a neutrophil chemoattractant that increases during systemic inflammation. C3a and C5a increase interleukin (IL)-8 secretion by endothelial cells, further attracting neutrophils.

More recently, the lectin-related complement activation pathway has also been shown to be involved in IgAVN and IgAN, as IgA can activate mannan-related lectins[43,44]. In contrast, IgA cannot activate the classic pathway and the main activator of the classic pathway, C1q, which is not present in immune complexes[45].

TLR activation and B cell proliferation

Another mechanism considered to be responsible for IgAV injury is the hyperreactivity of B and T cells in response to specific antigenic triggers. TLR signaling is the first line of defense against microbial infection. Hyperactivated TLR signaling causes cellular inflammatory infiltration that generates cytokines and autoantibodies, leading to autoimmune diseases[46,47].

TLRs are expressed in numerous cells, including kidney cells. There is increasing evidence to support the role for TLRs in autoimmune and inflammatory kidney diseases[22].

Donadio *et al*[48] showed children with IgAV that had significantly increased expression of mRNA encoding for TLR4, compared with healthy controls. TLR2 mRNA expression showed a borderline increase, while no difference was found in the expression of mRNA encoding for TLR3 and TLR9. Regulatory T cells (Treg) expressing the transcriptional factor FoxP3 play a potent anti-inflammatory role. Defective expression of FoxP3 mRNA and reduced expression of transforming growth factor- β 1 mRNA were also demonstrated, indicating a defective activity of Treg cells in IgAV[48].

However, it is still unclear if TLR expression is also associated with IgAVN development.

The role of anti-endothelial cell antibodies in IgAVN

Anti-endothelial cell antibodies (AECAs) are a heterogeneous group of antibodies directed to human endothelial cell antigens. A role of these antibodies in IgAVN has been hypothesized[49]. According to the hypothesis, tumor necrosis factor- α can increase the binding of IgA1 AECAs to endothelial cells. The latter produce IL-8, leading to neutrophil migration[50].

The interaction between IgA1 AECAs and Fc α RI on neutrophils results in the release of LTB₄, inducing neutrophil recruitment, reactive oxygen species release, neutrophil extracellular traps accompanied by the cell death (NETosis) and antibody-dependent cellular cytotoxicity. All this leads to vascular injury in the final analysis[51].

Other possible pathogenic mechanisms of IgAVN

Other pathogenetic mechanisms underlying IgAVN need to be further investigated. Masuda *et al*[52] showed that nephritis-associated plasmin receptor, a nephritogenic antigen for acute poststreptococcal glomerulonephritis, might have a pathogenic role in a subgroup of patients with IgAVN[52].

In a study by Davin *et al*[29], elevated plasma levels of IgE were found more commonly in patients with IgAN, but the pathogenetic role of IgE has not yet been clarified. In fact, mast cells are not usually present in the mesangium[24].

Eosinophil activation, higher levels of eosinophil cationic protein (ECP) in serum, and renal α -smooth muscle (α -SMA) expression have also been proposed as playing a role in the pathogenesis of IgAVN[25].

Observations indicate that enhanced renal α -SMA expression could be an early histological marker of IgAN progression. Similarly, increased expression of α -SMA in the tubule-interstitial region, but not in glomeruli, has been associated with bad prognosis[26].

BIOMARKERS

It is currently not possible to predict and identify which children may develop chronic kidney damage from onset. Some serum and urine markers can identify IgAV patients with or without renal involvement and in predicting the severity of renal inflammation to avoid chronic damage[53,54]. Measuring biomarkers in urine has many advantages: Samples are easy to collect using non-invasive methods; urine reflects damages in renal parenchyma, unlike blood, which comes into contact with many organs and organ systems; the number of different core proteins in the urine is lower than in blood [55]. In a prospective, multicenter study, Pillebout *et al*[54] identified biomarkers that may identify IgAVN at the onset of the disease: Serum Gd-IgA1 level, urine IgA, IgG, IgM, IL-6, IL-8, IL-10, and IgA-IgG and IgA-sCD89 complex levels[54]. A systematic literature review performed by Sugino *et al*[56] identifies that some clinical and urinary biomarkers potentially correlate with the presence and severity of IgAVN in children. The most promising preclinical urinary biomarkers in predicting nephritis are: Kidney injury molecule-1 (KIM-1), monocyte chemotactic protein-1 (MCP-1), N-acetyl- β -glucosaminidase (NAG), and angiotensinogen. Urinary KIM-1, MCP-1, and NAG correlate with the disease severity of nephritis (4). However, none of them prove to be established markers of disease. Further studies are needed to verify whether preclinical markers are better than the currently used ones (24-h urinary protein values, urinary protein:creatinine ratio and urinary albumin concentration)[55].

TREATMENT

Figure 1 illustrates the integration of the pathogenesis diagram with the drug treatment diagram to reveal the supporting mechanism of the drugs.

Decisions regarding the treatment of IgAVN are challenging due to the large percentage of patients with a positive prognosis and the uncertain clinical progression of single patients. Unfortunately, evidence-based treatment is not yet

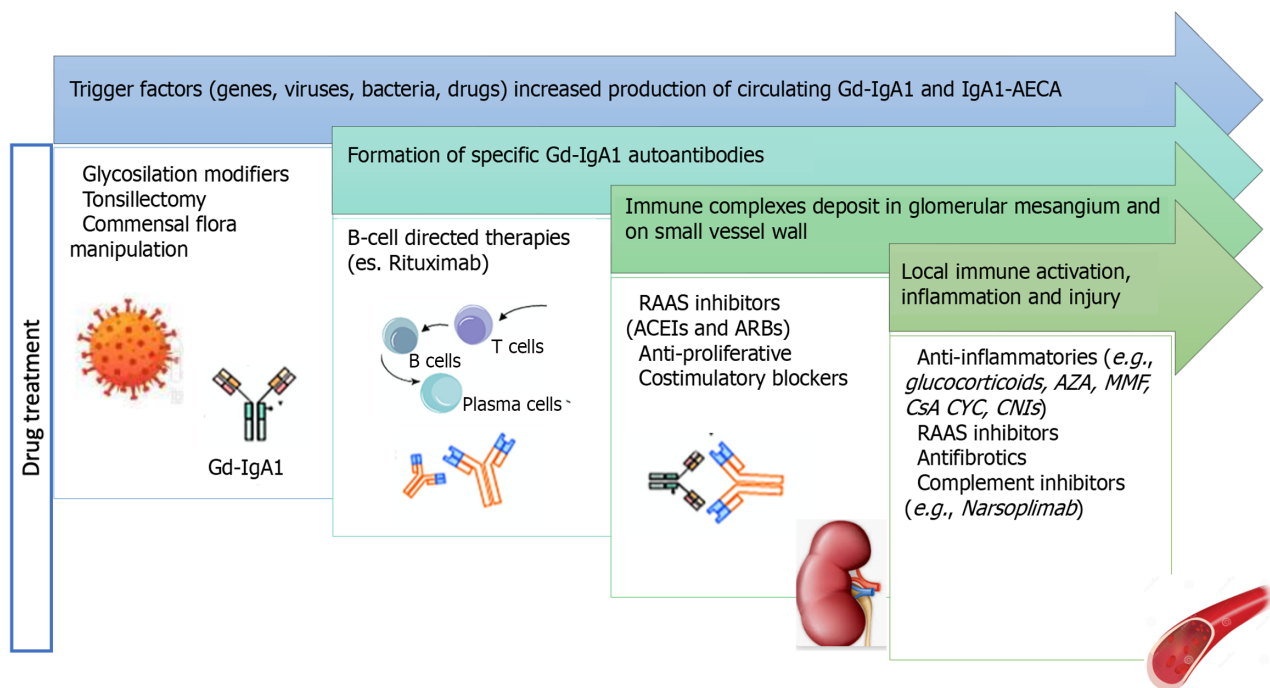


Figure 1 Pathogenesis and drug treatment for immunoglobulin A vasculitis and nephritis. Gd-IgA1: Galactose-deficient-immunoglobulin A; AECA: Anti-endothelial cell antibodies; RAAS: Renin-angiotensin-aldosterone system; ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; AZA: Azathioprine; MMF: Mycophenolate mofetil; CsA: Cyclosporine A; CYC: Cyclophosphamide; CNIs: Calcineurin inhibitors.

available even for the most serious event[1]. In several retrospective studies, delayed therapy has been related to a bad outcome. Therefore, despite the risk of spontaneous remission, it may be recommended that severely affected patients be treated as soon as possible.

Recently, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have mainly highlighted that the treatment of IgAVN remains a matter of debate and, in the absence of sufficient long-term data, have recommended that it should be treated in the same way as in patients with non-severe forms of isolated IgAN. However, the KDIGO guidelines do not take into account the more acute onset of IgAVN with more aggressive lesions in renal histology[57]. According to KDIGO guidelines, IgAVN patients should first receive a supporting care including routine modification (smoking cessation, weight control, regular exercise and dietary sodium restriction), blood pressure control and a course of renin-angiotensin system (RAS) blockers without immunosuppressive drugs or steroids. In the opinion of experts, this approach can result in the undertreatment of glomerular inflammation, mainly because acute and potentially aggressive glomerular inflammation goes untouched or its immunosuppressed treatment is postponed for several months.

On the contrary, European treatment guidelines consider IgAN and IgAVN as two distinct entities and suggest oral steroids as a first line therapy in IgAVN. In this regard, the German Society of Pediatric Nephrology has recently suggested an early treatment approach for patients with important kidney involvement. Following this treatment suggestion, IgAVN patients with nephritic syndrome, nephrotic syndrome, or glomerular cellular growths will receive an initial standardized corticosteroid- based treatment regimen for 2 mo, followed by an additional immunosuppression in patients with inadequate response after 3-6 mo from the start of treatment[58].

Corticosteroids, intravenous or oral, are part of most treatment regimens, and there is some evidence of their positive result on the long-term outcome of adult IgAN patients. Similarly, other immunosuppressive therapies, such as azathioprine (AZA), mycophenolate mofetil (MMF), cyclosporine A (CsA), or rituximab, have been shown to be effective in individual cases or in small series of patients. Cyclophosphamide (CYC) has also been used for more severe manifestations of IgAN (Table 2)[6]. In conclusion, given the rare nature of severe IgAVN, there is a necessity to standardize the diagnostic and therapeutic approach at least nationally, but ideally multinationally, in order to gain more expertise and move to evidence-based treatment. Future treatment strategies should be evaluated in large multicenter trials. Figure 2 summarizes the treatments available for IgA vasculitis and nephritis.

Corticosteroids

Several studies highlight a potential beneficial impact of corticosteroids in IgAVN. Oral prednisolone and/or pulsed methylprednisolone should be used as the earliest treatment in those cases with mild-moderate IgAVN[6]. A randomized, placebo-controlled trial showed that IgAVN was resolved more quickly in children treated with prednisone than in those treated with placebo. However, the study offered outcome data only 6 mo after randomization. Hence, it is unknown whether prednisone treatment reduced the number of cases with persistent IgAVN or simply encouraged a more rapid resolution of the renal disease compared with the placebo[59]. Kim *et al*[60] showed that corticosteroid exposure significantly reduced serum Gd-IgA1 levels, which are associated with the pathophysiology of IgAVN[60].

Table 2 Treatments according to European treatment guidelines

		Class of drugs	Ref.
Mild IgAVN	First line	Corticosteroids: Oral prednisolone	[60-62]
	Second line (or corticosteroid-sparing agent)	Immunosuppressive therapies: Pulsed methylprednisolone or AZA or MMF, CsA	[6,71,72]
Moderate IgAVN	First line	Corticosteroids: Oral prednisolone and/or pulsed methylprednisolone	[6,60-62]
	Second line (Cortico-dependent and cortico-resistant forms of IgAVN)	Immunosuppressive therapies: AZA, MMF, CYC iv	[71,72]
Severe IgAVN	First line	Immunosuppressive therapies + corticosteroids: AZA or MMF or CYC, CNIs (<i>Cyclosporin A</i> or <i>Tacrolimus</i>), <i>Rituximab</i> , <i>Plasmapheresis</i>	[64-66,74-77]
New drugs: <i>Dapsone</i> , <i>Narsoplimab</i> , <i>Sparsentan</i>			[81,82]
RAS blockers (ACEIs and ARBs) should be used in IgAVN as soon as possible			[78-80]

ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; IgAVN: Immunoglobulin A vasculitis nephritis; AZA: Azathioprine; MMF: Mycophenolate mofetil; CsA: Cyclosporine A; CYC: Cyclophosphamide; CNIs: Calcineurin inhibitors.

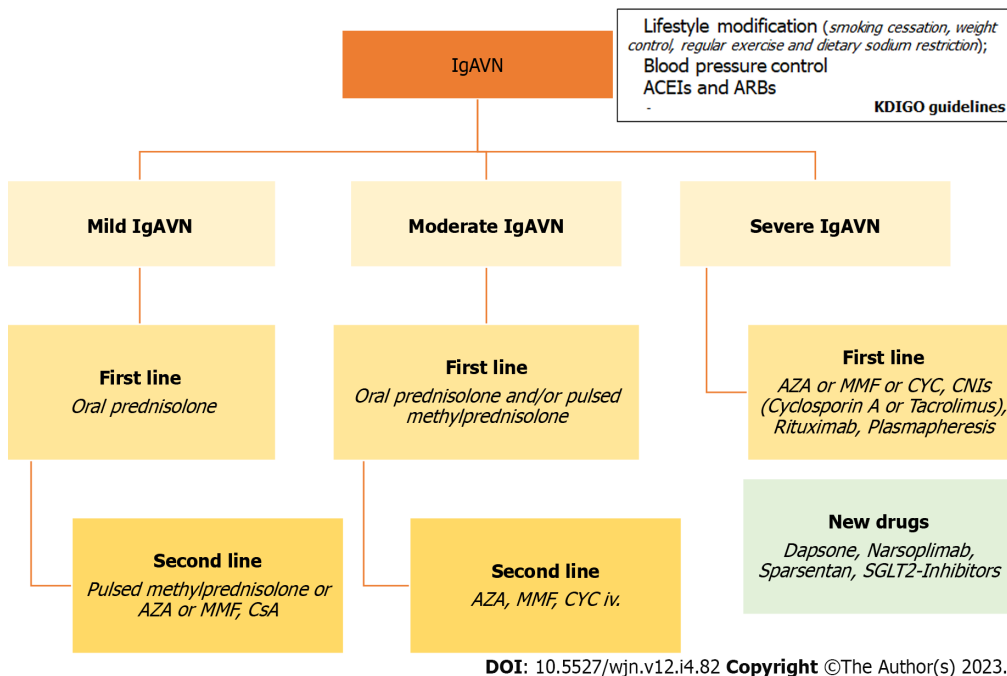


Figure 2 Therapeutic algorithm for immunoglobulin A vasculitis and nephritis. ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; IgAVN: Immunoglobulin A vasculitis nephritis; AZA: Azathioprine; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; CNIs: Calcineurin inhibitors; CsA: Cyclosporine A.

However, no evidence has been found that early treatment with steroids could prevent nephritis in IgAV patients and reduce the risk of proteinuria in the following 12 mo[61].

Other immunosuppressive therapies

In the cortico-dependent and cortico-resistant forms of IgAVN, other immunosuppressive treatments, such as calcineurin inhibitors (CNIs), AZA, MMF, CYC, rituximab and plasmapheresis can be considered. AZA, MMF or intravenous CYC can be used in the first- or second-line management of moderate-severe IgAVN[6].

CNIs should be considered a hopeful agent for the treatment of severe IgAVN. The two CNIs currently on the market are CsA and tacrolimus. CsA was found to be effective in improving histological lesions and proteinuria in IgAVN patients[62,63]. In a pilot study of 20 IgAVN children, 12 of whom received tacrolimus treatment reached complete remission; eight achieved partial remission at the end of 6 mo[64].

Current data are not in favor of CYC use in IgAVN because no statistically significant differences were found in the group of patients treated with this immunosuppressive drug compared to the group treated with high doses of corticosteroid[65,66]. CsA or oral CYC cannot be routinely recommended in moderate IgAVN. Intravenous CYC with pulsed methylprednisolone and/or oral prednisolone are also required as an earliest treatment in patients with IgAVN[6]. AZA

appeared to be an effective steroid-sparing drug. This has allowed all steroid-dependent patients to go steroid-free. No formal guidelines are available for the duration of treatment. In studies no patient has had any adverse events associated with AZA therapy[67,68].

MMF should be suggested patients with IgAVN, especially if proteinuria still remains after an initial steroid course and despite antiproteinuric treatment[69,70]. A current meta-analysis has, in fact, reported results combining eight studies and proposed that patients with IgAN treated with MMF had higher remission than the control group[71]. In association with steroid therapy, AZA and MMF can be used as a maintenance treatment in those patients with severe IgAVN[6].

Data on the use and efficacy of the anti-CD20 monoclonal antibody rituximab in patients with IgAVN are still limited. A few case reports have recommended that rituximab could be successful in IgAVN in both pediatric and adult ages, especially if other oral immunosuppressive treatments have not been able to induce remission[72,73].

Finally, there is plasmapheresis, which can be used as a rescue therapy in cases of rapid progression to renal failure or persistent nephrotic syndrome. Interestingly, early plasmapheresis has been useful in some patients even without additional immunosuppression[74,75].

RAS blockers

Numerous data suggest that RAS blockers such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be used in IgAVN and as soon as possible. Prospective randomized trials have shown that the use of these drugs improves long-term renal issues in children and adults and prevents/Limits secondary glomerular injury in patients with persistent proteinuria[76-78].

New drugs

Dapsone is a drug that could be considered for the treatment of IgAVN because it can suppress the development of toxic-free radicals by neutrophils. It also reduces the output of IgA antibodies, an essential phenomenon in the pathophysiology of IgAVN[79,80].

A phase II study recently demonstrated the safety, tolerability, and efficacy of narsoplimab, a novel Mannan-binding lectin-associated serine proteinase 2 inhibitor. It is a humanized monoclonal antibody that inhibits the lecithin pathway target of the complement system and seems to result in a clinically significant reduction in proteinuria and the stability of renal function as evaluated by eGFR in high-risk patients with IgAN[81].

A clinical trial is being conducted to evaluate the use of sparsentan as a potential first-line treatment in patients with newly diagnosed IgAN who have not received previous treatment with RAS blockers. Treatment response will be based on endpoints of proteinuria and GFR and will be assessed by changes from the baseline compared to another treatment [76].

Many studies have shown the renoprotective role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in early to advanced diabetic kidney disease. Recent evidence show that SGLT2 inhibitors are similarly renoprotective in non-diabetic chronic kidney disease, such as IgAN, in a wide range of eGFR of 25-75 mL/min/1.73 m² and albumin/creatinine ratio of 200-5000 mg/g[82,83].

INTERVENTIONS FOR PREVENTING IGAVN

According to a recent Cochran study on the prevention and treatment of IgAVN, studies have shown no benefit of prednisone with respect to placebo or no treatment in preventing persistent kidney disease in children without or with little kidney disease at the time of onset[61].

CONCLUSION

According to the European SHARE initiative, only follow-up is required for patients with microscopic haematuria, no renal disorder and proteinuria, or with non-persistent mild or moderate proteinuria. In the case of severe proteinuria or impaired GFR, a paediatric nephrologist must be consulted and a renal biopsy performed. In the case of mild IgAVN, oral prednisolone should be used as a first-line treatment. In some patients with persistent proteinuria, the addition of AZA or MMF, CsA or pulsed methylprednisolone, may be used as a second-line treatment or as a corticosteroid- sparing agent. For patients with moderate IgAVN, oral prednisolone and/or pulsed methylprednisolone should be used as earliest treatment. Addition of AZA, MMF or intravenous CYC may also be used in the first- or second-line treatment of moderate nephritis, according to the histological findings in the kidney biopsy. For severe IgAVN, intravenous CYC with pulsed methylprednisolone and oral prednisolone should be used as a first-line treatment. AZA/MMF plus steroid therapy can be used as a second life[6].

FOOTNOTES

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Transcending boundaries: Unleashing the potential of multi-organ point-of-care ultrasound in acute kidney injury

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Abstract

Acute kidney injury (AKI) is a clinical syndrome characterized by a rapid increase in serum creatinine levels or a decrease in urine output or both. In spite of thorough history-taking, physical examination, and laboratory analysis, there are limitations in the diagnostic process and clinical monitoring of AKI. Point-of-care ultrasonography (POCUS), a limited ultrasound study performed by clinicians at the bedside, has emerged as a valuable tool in different clinical settings. In this discussion, we explore the potential of POCUS performed by nephrologists to address specific questions encountered in the diagnosis and management of AKI patients. POCUS not only aids in excluding hydronephrosis but also provides real-time insights into hemodynamics, enabling formulation of individualized treatment plans. Further studies are required to assess the impact of multi-organ POCUS on pragmatic patient outcomes related to AKI, as well as its potential in risk stratification and identification of different levels of AKI severity and pathophysiological signatures.

Key Words: Ultrasound; Point-of-care ultrasonography; Doppler; Venous excess Doppler ultrasound; Congestion; Hemodynamics; Heart failure; Nephrology

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Core Tip: Point-of-care ultrasound, not limited to kidney is a valuable addition to nephrologists' toolkit, which enhances diagnostic accuracy and guides therapy when properly integrated with clinical and laboratory parameters.

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INTRODUCTION

Acute kidney injury (AKI) is characterized by a rapid rise in serum creatinine or decrease in urine output or both. It is a clinical syndrome resulting from a variety of hemodynamic, toxic, and structural insults to the kidney, poses a challenge in terms of diagnosis and clinical monitoring, impacting patient outcomes[1,2]. Despite thorough history-taking, physical examination, and laboratory analysis, there are gaps in the diagnostic process and management of AKI. Point-of-care ultrasonography (POCUS) is a limited bedside ultrasound study performed by clinicians as an adjunct to physical examination intended to answer focused clinical questions. There is a growing body of evidence supporting the effectiveness of POCUS in diverse clinical scenarios[3]. As a result, its integration into medical school curricula is becoming more prevalent, and subspecialties are actively working to keep pace with this advancement. In this review, we explore the potential of nephrologist-performed POCUS in addressing specific diagnostic and management questions in AKI patients. From ruling out hydronephrosis to providing real-time hemodynamic insights, integrating POCUS into patient evaluation allows for a comprehensive assessment and the development of individualized treatment plans.

DEFINITION AND CLASSIFICATION OF AKI

According to the Kidney Disease Improving Global Outcomes clinical practice guideline, AKI is defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or increase to ≥ 1.5 times the baseline value within the past 7 d or urine volume < 0.5 mL/kg/h for a duration of 6 h[4]. AKI can be classified into three main categories based on etiology: Hemodynamic causes, urinary tract obstruction, and intrinsic renal diseases. Hemodynamic causes are associated with impaired renal perfusion, while urinary tract obstruction refers to blockages that prevent normal urine flow. Intrinsic renal diseases involve conditions affecting the kidney's internal structures, such as glomerulonephritis or tubulointerstitial diseases. It is important to highlight that what was previously termed *prerenal* AKI is now referred to as *hemodynamic* AKI. While *prerenal* logically suggests any insult occurring before the kidney, it is often misunderstood in clinical practice and used synonymously with volume depletion-related AKI. This narrow interpretation disregards other important factors, such as congestive nephropathy resulting from volume excess or conditions associated with compromised blood supply or renal vasoconstriction. Therefore, the term *hemodynamic* AKI is more comprehensive and encompasses all conditions that can adversely affect renal perfusion. Furthermore, it is noteworthy that while above classification provides a basic framework, AKI etiology in clinical practice is often more complex, with multiple pathologies coexisting. In certain contexts, it may be more appropriate to use a syndrome-based nomenclature, such as cardiorenal, hepatorenal, hepatocardiorenal, or sepsis-associated AKI, to better describe the underlying conditions[1,5]. To maintain simplicity, we will describe the role of POCUS using broad categories of AKI in this review.

POCUS IN HEMODYNAMIC AKI

Accurate assessment of fluid status, or more specifically, hemodynamic assessment, is crucial in the management of hemodynamic AKI. Unfortunately, conventional physical examination lacks sensitivity in this regard, and the introduction of POCUS has significantly improved bedside evaluation[6,7]. POCUS, when performed and interpreted by a skilled practitioner, provides comprehensive information about the entire hemodynamic circuit, and enables informed decision-making regarding the requirement for volume resuscitation or decongestive therapy. The outdated approach of administering intravenous fluids in a trial-and-error manner when volume status is uncertain is no longer justifiable in the era of POCUS. This holds significant importance, especially considering the growing recognition of the detrimental effects of fluid overload on renal and overall outcomes in conditions such as heart failure and critical illness. For instance, in a recent systematic review and meta-analysis including 31076 critically ill patients, for every liter increase in positive fluid balance, the risk of mortality increased by a factor of 1.19 [95% confidence interval (CI): 1.11-1.28][8]. Although association does not imply causation, it is crucial to approach intravenous fluids as medications and administer them only when there is a clear indication. Notably, a recent clinical trial demonstrated the safety of a restrictive fluid management strategy in patients with septic shock, as compared to standard care (*i.e.*, liberal strategy). Although the outcome did not show superiority in the restrictive group, it is worth mentioning that the liberal group received significantly less fluid compared to previous studies that demonstrated harm, with a median of 3.8 liters[9]. In the context of heart failure, the significance of venous congestion causing renal dysfunction *i.e.*, congestive nephropathy is often overlooked in comparison to the forward flow hypothesis, which implicates inadequate cardiac output. However, multiple studies have indicated that elevated central venous pressure (CVP) is associated with deteriorating renal function, even in the presence of preserved cardiac index[10,11]. Conversely, a decrease in glomerular filtration rate (GFR) is observed in heart failure primarily in cases of extremely low cardiac output. For example, in one study, patients

were categorized into three groups based on their cardiac index (CI): CI > 2.0 L/min/m² (group A), CI: 1.5 to 2.0 L/min/m² (group B), and CI < 1.5 L/min/m² (group C). While all groups exhibited a decrease in the renal fraction of cardiac output and renal blood flow, a significant reduction in GFR was observed only in group C[12].

Our group has previously introduced a goal-directed POCUS strategy for hemodynamic assessment known as the *pump, pipes, and the leaks*[13]. The pump refers to focused cardiac ultrasound, pipes represent ultrasound evaluation of the inferior vena cava (IVC) and venous Doppler, while the leaks involve assessing extravascular lung and abdominal fluid (Figure 1).

The pump

The performance and efficiency of the heart directly impact blood flow, organ perfusion, and function. As such, a comprehensive hemodynamic assessment involves evaluation of various cardiac parameters that determine forward flow as well as backward congestion. A subjective assessment of left ventricular (LV) size and motion can provide a qualitative estimate of ejection fraction (EF). This *eyeballing* method has proven to be reasonably accurate when performed by non-cardiologists with minimal training[14]. Additionally, other parameters such as pericardial effusion, valvular dysfunction, and chamber enlargement can be evaluated. Right ventricular (RV) enlargement and interventricular septal flattening are associated with volume overload and/or pressure overload, resulting in a D-shaped LV appearance in the parasternal short axis cardiac view. RV enlargement is often accompanied by functional tricuspid regurgitation, which further contributes to RV overload and increased right atrial pressure (RAP), which can be estimated by IVC POCUS[15, 16]. Nephrologists trained in Doppler applications can assess stroke volume at the bedside by measuring LV outflow tract velocity time integral (LVOT VTI) providing insight into cardiac index, which can be used to distinguish between hypovolemia and euvolemia and low *vs* high cardiac output states (allows for differentiation between patients who would benefit from intravenous fluids and those who require vasopressors or inotropes). In select patients, LVOT VTI can also be used to determine fluid responsiveness, potentially avoiding excessive fluid administration. Furthermore, ability to perform Doppler POCUS enables the evaluation of LV filling pressures, aiding in the titration of diuretic therapy in outpatient settings. For example, in a study involving 1135 patients with heart failure with reduced EF, the group whose management was guided by assessing LV filling pressures and B-type natriuretic peptide levels exhibited a lower incidence of death [hazard ratio (HR): 0.45, $P < 0.0001$] and death or worsening renal function (HR: 0.49, $P < 0.0001$) compared to the standard care group during a median follow-up period of 37.4 mo[17]. Similarly, RV outflow tract Doppler and trans-tricuspid Doppler measurements offer valuable information on pulmonary artery pressures and may help distinguish between precapillary and postcapillary pulmonary hypertension[18-20]. By combining the measurement of LVOT VTI with these Doppler assessments, we can potentially identify patients with AKI who would benefit from further volume removal *vs* those who may require pulmonary vasodilator therapy. This approach allows for a more targeted and individualized treatment strategy based on the specific hemodynamic profile of each patient.

The pipes

IVC ultrasound: Estimating RAP using IVC size and collapsibility is a standard component of comprehensive echocardiography. In spontaneously breathing patients, the current guidelines recommend the following stratification for RAP. If the maximal anteroposterior diameter of IVC is less than 2.1 cm with more than 50% collapse during a sniff, RAP is estimated to be around 3 mmHg (ranging from 0 to 5 mmHg). If the IVC is larger than 2.1 cm and exhibits less than 50% collapse, RAP is recorded as 15 mmHg (ranging from 10 to 20 mmHg). In cases where the IVC parameters do not align with this classification, an intermediate value of 8 mmHg (ranging from 5 to 10 mmHg) is assigned. However, the correlation between IVC parameters and RAP measured through right heart catheterization is modest at best and may not be applicable to mechanically ventilated patients[21-23]. It is also unreliable in conditions such as intraabdominal hypertension. Moreover, IVC POCUS is susceptible to various technical challenges such as cylinder effect, limiting its practical usefulness, particularly when interpreted in isolation[24]. Nevertheless, the assessment of IVC can still serve as an indicator of fluid tolerance, as an engorged IVC often indicates elevated RAP in patients with a high likelihood of fluid overload. In other words, such patients have increased right-sided filling pressures and may not tolerate intravenous fluid administration.

Alternatives to IVC ultrasound: POCUS of other systemic veins such as the internal jugular vein (IJV) and superior vena cava (SVC) can be utilized for non-invasive estimation of RAP, particularly when the IVC is not accessible or unreliable (e.g., liver disease, abdominal surgery). Most clinicians are familiar with estimating jugular venous pressure through visual inspection of IJV, but it lacks sensitivity; the use of POCUS enables improved identification of the vein. In a recent study, an IJV maximal diameter of ≥ 1.2 cm or respiratory variation in diameter of $< 30\%$ showed specificity $> 70\%$ for elevated filling pressure (RAP ≥ 10 mmHg). Combining IJV POCUS with physical examination improved the combined specificity to 97% for RAP ≥ 10 mmHg[25]. In another study, less than 17% increase in the cross-sectional area of the right IJV with Valsalva maneuver predicted an elevated RAP (> 12 mmHg) with 90% sensitivity and 74% specificity[26]. In patients with cirrhosis, Leal-Villarreal *et al*[27] found that IJV POCUS predicts RAP better than IVC. Interestingly, satisfactory IVC images were not attainable in 18% of the cases[27]. SVC provides comparable information about RAP since it is another vessel that enters the right atrium like IVC. However, it's not routinely used in point of care settings as transesophageal echocardiography is generally needed to obtain reliable images of the vessel. Nevertheless, Doppler ultrasound of the SVC through the subcostal transthoracic window is emerging as a viable alternative[28].

Venous congestion assessment by Doppler ultrasound: The assessment of Doppler patterns in abdominal veins has been a subject of study for several decades. However, it was not until 2020 that Beaubien-Souligny *et al*[29] introduced the concept of venous excess ultrasound or Venous Excess Doppler UltraSound (VExUS), which has significantly transf-

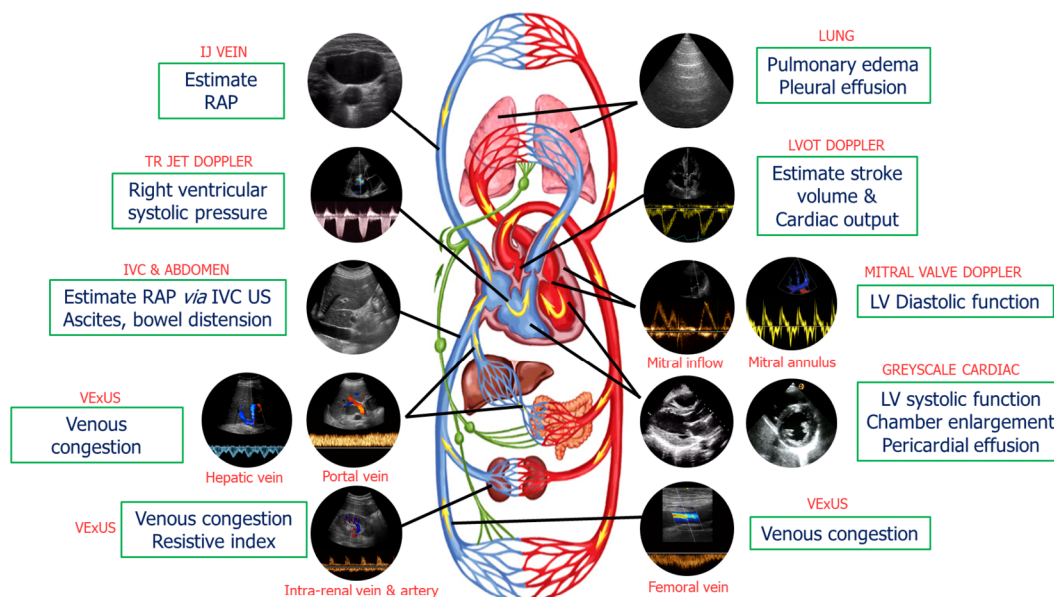


Figure 1 Common sonographic applications used by trained clinicians at the bedside in the evaluation of acute kidney injury. It is important to evaluate multiple points of the hemodynamic circuit instead of relying on isolated parameters. IJ: Internal jugular; RAP: Right atrial pressure; TR: Tricuspid regurgitation; IVC: Inferior vena cava; US: Ultrasound; VExUS: venous excess ultrasound; LV: Left ventricular; LVOT: Left ventricular outflow tract. Citation: Koratala A, Reisinger N. Point of Care Ultrasound in Cirrhosis-Associated Acute Kidney Injury: Beyond Inferior Vena Cava. *Kidney360* 2022; 3: 1965-1968. Copyright© 2022 by the American Society of Nephrology (corresponding author's prior open access publication).

formed our noninvasive evaluation of congestion at the bedside. Among their group of patients who underwent cardiac surgery, it was observed that the occurrence of significant flow abnormalities in two or more veins (hepatic, portal, and kidney parenchymal veins) combined with an enlarged IVC (≥ 2 cm) proved to be a more effective predictor of AKI risk (HR: 3.69; 95%CI: 1.65-8.24; $P = 0.001$) compared to isolated CVP measurements[29]. In other words, direct assessment of venous congestion using Doppler ultrasound offers more comprehensive information regarding congestive organ injury compared to isolated ultrasound of the IVC or IJV. Additionally, since these waveforms are dynamic in nature, VExUS serves as a valuable bedside tool for monitoring the effectiveness of decongestive therapy in real time[30-32]. **Figure 2** depicts the transformation of individual Doppler waveforms with increasing RAP as well as the VExUS grading system. It is important to highlight that VExUS is not limited to cardiac surgery or heart failure patients. A recent study by Rihl *et al*[33] demonstrated its applicability in an unselected cohort of patients admitted to the medical intensive care unit. The study found that patients who had reduction in their VExUS score through decongestive therapy had a significantly higher number of days free from renal replacement therapy at Day 28 compared to those who did not achieve a reduction (28 *vs* 15, $P = 0.012$). Moreover, CVP alone was unable to distinguish between patients with no/mild congestion and those with severe congestion[33]. VExUS is determined by both RAP and venous compliance, making it a comprehensive measure of venous congestion. Merely measuring RAP alone does not necessarily provide information about the extent of venous congestion.

Extended VExUS: The concept of E-VExUS, or extended VExUS, has been introduced to incorporate Doppler evaluation of additional veins like the internal jugular, SVC, splenic, and femoral veins[34]. **Figure 3** depicts components of E-VExUS. This extension is particularly useful when the primary veins have certain limitations (such as hepatic and portal veins in cirrhosis or intrarenal veins in advanced kidney disease). Like the components of the original VExUS, these veins have also been studied individually and demonstrated their usefulness in identifying elevated RAP[28,35-38]. Lately, there has been a surge in interest regarding femoral vein Doppler because of its relatively straightforward image acquisition process. In a recent study, the accuracy of both VExUS score and femoral vein Doppler in detecting venous congestion was reported as 80.37 (95%CI: 71.5-87.4) and 74.7 (95%CI: 65.4-82.6), respectively[39]. Nevertheless, the use of E-VExUS is still in the early phases of implementation, and further data are required to determine its clinical utility in routine practice.

Renal arterial resistive index: In principle, the measurement of intra-renal arterial resistive index (RI) is an appealing method to assess renal perfusion, and it has been studied in various clinical scenarios such as heart failure, septic shock, and hepatorenal syndrome, showing some usefulness[40-43]. The RI is calculated using the formula (peak systolic velocity-end diastolic velocity)/peak systolic velocity within a given cardiac cycle (**Figure 4A**). However, the RI is influenced by multiple renal and non-renal variables including pulse pressure, heart rate, arteriosclerosis, vasoconstriction, venous congestion, underlying chronic kidney disease, valvular diseases like aortic stenosis, as well as medications, which limits its practical utility[44]. RI has also been a subject of interest in the evaluation of renal artery stenosis (RAS), but its diagnostic value remains non-specific. In our clinical practice, we rely on computed tomography (CT) or magnetic resonance angiography to evaluate patients with uncontrolled hypertension and a high suspicion for

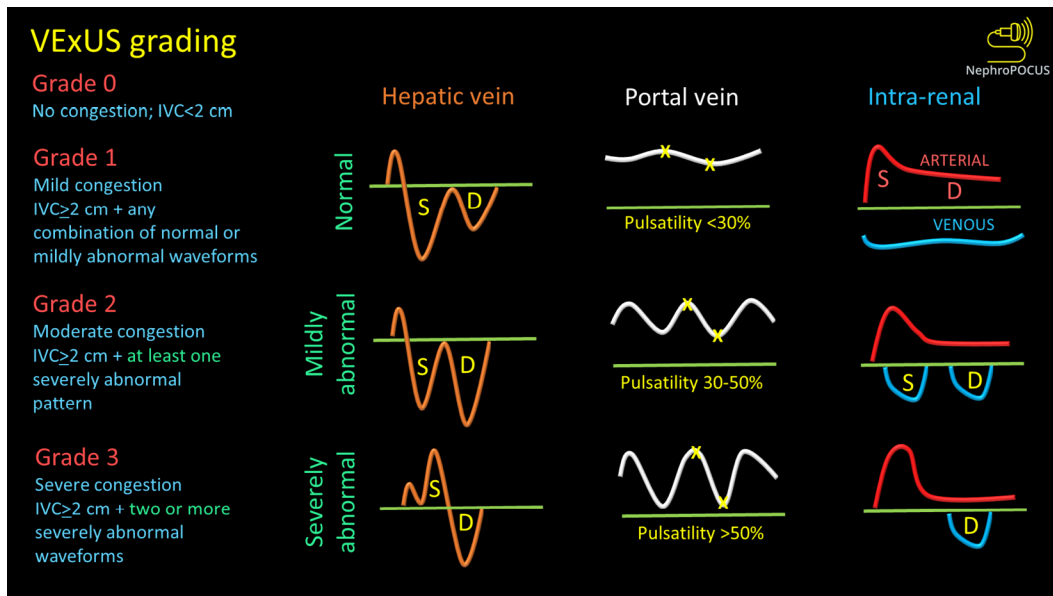


Figure 2 VexUS (Venous Excess Doppler UltraSound) grading system: When the diameter of inferior vena cava is > 2 cm, three grades of congestion are defined based on the severity of abnormalities on hepatic, portal, and renal parenchymal venous Doppler. Hepatic vein Doppler is considered mildly abnormal when the systolic (S) wave is smaller than the diastolic (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% to 50%, and severely abnormal when it is ≥ 50%. Asterisks represent points of pulsatility measurement. Renal parenchymal vein Doppler is mildly abnormal when it is pulsatile with distinct S and D components, and severely abnormal when it is monophasic with D-only pattern. Figure adapted from NephroPOCUS.com with permission (corresponding author's educational website)-<https://nephropocus.com/2021/10/05/vexus-flash-cards/>.

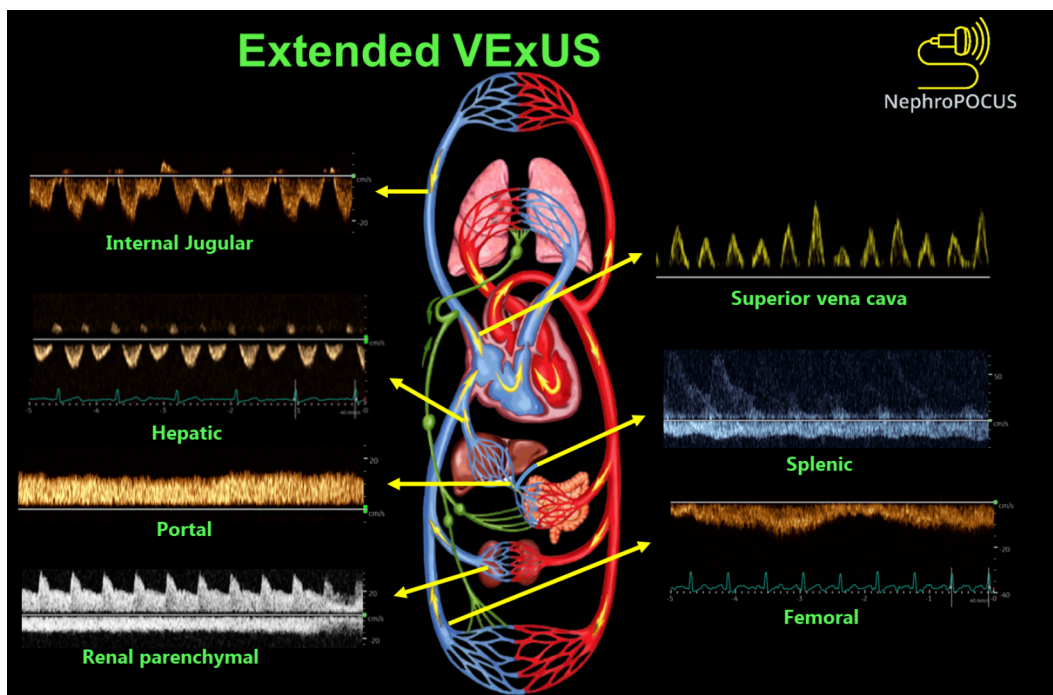
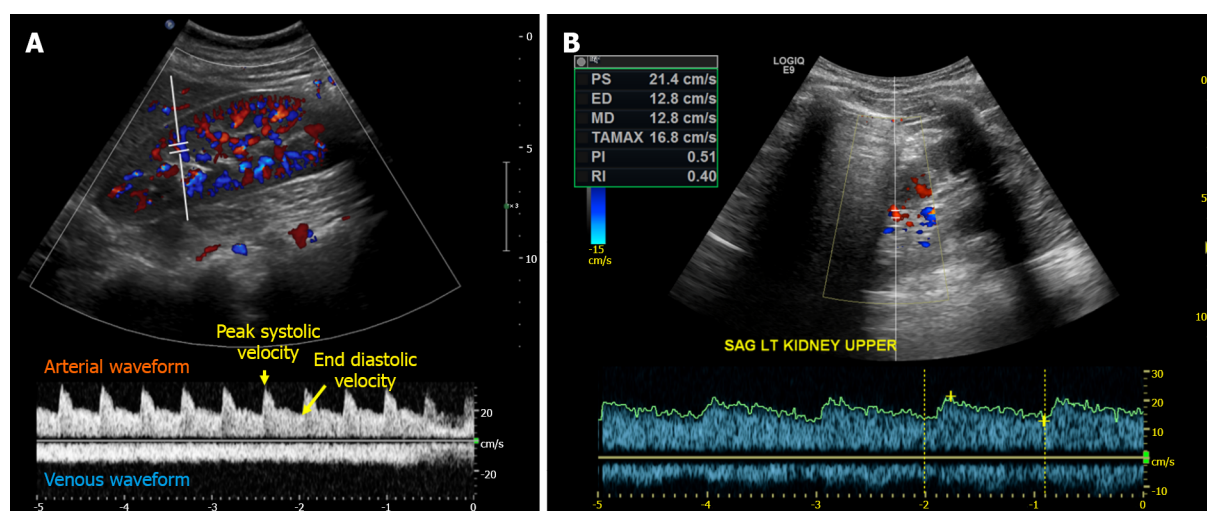


Figure 3 Doppler components of extended VexUS examination. Figure adapted from NephroPOCUS.com with permission (corresponding author's educational website)-<https://nephropocus.com/2022/11/28/hemodynamic-pocus-in-cirrhosis-think-beyond-the-ivc/>.

RAS instead of POCUS. However, in some cases of RAS, a *Tardus parvus* waveform may be noted by the POCUS-performing physician, which should prompt further investigation. It is characterized by a slow upstroke and rounding of the systolic peak, relatively specific for RAS when found, resulting from proximal stenosis and reduced blood flow (Figure 4B). Additionally, based on our experience, there is significant variability both between different operators and within the same operator when reporting the RI, making it less reliable for monitoring response to therapeutic interventions in the point of care settings. Moreover, intrarenal Doppler in general is technically challenging to perform in



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Figure 4 Intrarenal Doppler demonstrating normal waveforms, Tardus Parvus waveform in a case of renal artery stenosis. A: Normal waveforms; B: Tardus Parvus waveform.

critically ill patients. On the contrary, intra-renal venous Doppler is a more reproducible and less error-prone method due to its qualitative nature, which involves waveform analysis without the requirement for precise measurements. Moreover, venous congestion may explain the elevated RI observed in patients with volume overload, as it increases the resistance to arterial diastolic flow.

The leaks

POCUS is a sensitive bedside tool to detect extravascular lung water and ascites, both of which have important management implications in the treatment of AKI (*e.g.*, determine the amount of ultrafiltration in patients requiring renal replacement therapy, titrate diuretic dosing, gauge fluid tolerance when contemplating intravenous fluid therapy or assess the need for therapeutic paracentesis). In a systematic review and meta-analysis including a total of 8 studies reporting on 2787 patients, lung POCUS was found to be more sensitive (91.8% *vs* 76.5%) and specific (92.3% *vs* 87.0%) than chest radiography for the detection of cardiogenic pulmonary edema[45]. Similarly, lung POCUS has been shown to detect small pleural effusions with a higher diagnostic accuracy than lateral decubitus chest radiography[46]. With respect to ascites, the superiority of ultrasound to physical examination and radiography has been long recognized[47]. Notably, unlike Doppler ultrasound, both these sonographic applications are much easier to learn with short training.

Figure 5 provides an Overview of common ultrasound findings in nephrology-relevant hemodynamic phenotypes.

POCUS IN INTRINSIC RENAL AKI

The usefulness of POCUS in determining the underlying cause of intrinsic AKI is limited. Parameters such as cortical echogenicity, thickness and renal length can provide some insights when considered in the appropriate clinical context but lack specificity (Figure 6)[48]. For instance, in cases where the baseline serum creatinine is unavailable, a small kidney size and increased cortical echogenicity may suggest a lower likelihood of treatable disease[49]. Conversely, enlarged kidneys with preserved parenchymal thickness and increased cortical echogenicity must prompt further investigation for infiltrative diseases like amyloidosis and malignancy, although these findings alone are not diagnostic. Of note, increased cortical echogenicity is seen in any renal parenchymal disease, regardless of acute or chronic process (*e.g.*, acute tubular necrosis, acute interstitial nephritis, acute glomerulonephritis, and chronic kidney disease)[50].

POCUS IN OBSTRUCTIVE AKI

Clinicians skilled in POCUS can easily identify urinary obstruction through bedside POCUS, leading to prompt diagnosis and timely intervention to relieve the obstruction, thereby preventing a decline in GFR. In one study, internist-performed POCUS demonstrated a sensitivity of 90% and a specificity of 100% for urinary tract obstruction in patients with AKI. Furthermore, the negative predictive value was 99%, indicating that it is a valuable tool that can potentially reduce the need for departmental ultrasound[51]. Similarly, in a study performed in the emergency setting, when compared to the consensus radiology interpretation of POCUS as the reference standard, emergency physicians demonstrated an overall sensitivity of 85.7% (95%CI: 84.3%-87.0%), specificity of 65.9% (95%CI: 63.1%-68.7%), positive likelihood ratio of 2.5 (95%CI: 2.3-2.7), and negative likelihood ratio of 0.22 (95%CI: 0.19-0.24) for detecting hydronephrosis[52]. On a note of

	Underfill (volume depletion)	Overfill	Systemic vasodilation
 Lung US	A-lines (horizontal artifacts)	- B-lines (vertical artifacts) - Pleural effusions	A-lines
 Cardiac US	- Hyperdynamic LV - Low stroke volume (estimated by LV outflow tract velocity time integral) - Relatively preserved right and left ventricular ratio (RV cavity is less than two-thirds of the LV in apical view) - Small, collapsible IVC (suggestive of low RAP)	- Decreased LV systolic motion (if systolic heart failure is the etiology) - Stroke volume low (in systolic heart failure) or high-normal - Dilated right ventricle - Interventricular septal flattening on short axis view (predominantly in diastole [volume overload] or both systole and diastole [pressure overload]) - Plethoric IVC (high RAP)	- Hyperdynamic LV - Supra-normal stroke volume (high output state) - Relatively preserved right and left ventricular ratio - Small, collapsible IVC
 VExUS	- Not indicated when the RAP is not elevated - Otherwise, expected to be normal. Hepatic vein Doppler may show fusion of S and D-waves	- Hepatic vein: S-wave < D-wave or S-reversal - Portal vein: Increased pulsatility - Renal parenchymal vein: Increased pulsatility, S-reversal	- Not indicated if IVC is small - In patients with cirrhosis and portal hypertension, portal vein can be pulsatile without an elevated RAP
 Additional points	- Above phenotypes are not exclusive; can co-exist in the same patient depending on the clinical scenario - Plethoric IVC could be due to volume or pressure overload; exclude pulmonary embolism, pericardial effusion - IVC can be small despite high right atrial pressure in intra-abdominal hypertension - Suboptimal/off-axis cardiac views are a frequent source of error in estimating stroke volume and chamber size		

Figure 5 Overview of common ultrasound findings in nephrology-relevant hemodynamic phenotypes. Systemic vasodilation is frequently seen in patients with liver cirrhosis or early sepsis and renal dysfunction. Underfill phenotype primarily denotes volume depletion. IVC: Inferior vena cava; LV: Left ventricle; RAP: Right atrial pressure; US: Ultrasound; VExUS: Venous excess Doppler ultrasound. Citation: Taleb Abdellah A, Koratala A. Nephrologist-Performed Point-of-Care Ultrasound in Acute Kidney Injury: Beyond Hydronephrosis. *Kidney Int Rep* 2022; 7: 1428-1432. Copyright© 2022 International Society of Nephrology. Published by Elsevier Inc. (corresponding author's prior open access publication).

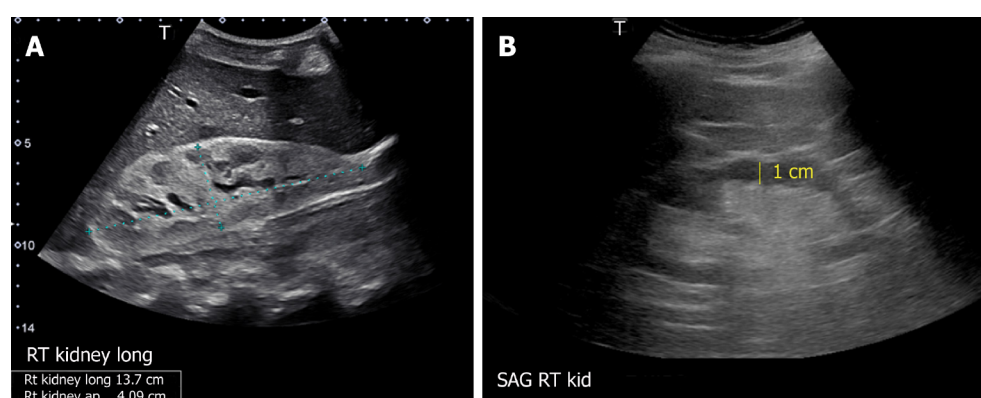


Figure 6 Renal sonogram demonstrating (A) large hyperechogenic kidney in a patient with multiple myeloma and (B) thin parenchyma approximately 1 cm in a patient with chronic kidney disease (normal parenchymal thickness: 1.5-2 cm). Citation: Koratala A, Bhattacharya D, Kazory A. Point of care renal ultrasonography for the busy nephrologist: A pictorial review. *World J Nephrol* 2019; 8: 44-58. Copyright© The Author(s) 2019. Published by Baishideng Publishing Group Inc. (corresponding author's prior open access publication).

caution, novice POCUS users should be aware of common ultrasound findings that can mimic hydronephrosis, including parapelvic cysts, extrarenal pelvis, and vascular malformations[53]. Figure 7 illustrates sonographic appearance of hydronephrosis and its qualitative grading. POCUS also allows timely identification of urinary bladder abnormalities such as urine retention, blocked or misplaced Foley catheter, urinary stones, masses, and prostatomegaly[50].

CONCLUSION

Multi-organ POCUS serves as a valuable complement to physical examination when evaluating AKI. While the use of POCUS by nephrologists has gained attention, several practical challenges exist. Currently, only a small number of nephrology fellowship programs provide comprehensive training in diagnostic POCUS beyond kidney ultrasound[54]. A significant barrier to widespread training is the limited availability of faculty who are proficient in ultrasound and have dedicated time for teaching. It is crucial for professional societies to collaborate in developing standardized guidelines, competency standards, and methods for ongoing training to support POCUS training in nephrology. While current studies mainly focus on initial training, additional research is needed to determine the optimal strategies for longitudinal training to maintain proficiency in POCUS skills. Additionally, while POCUS examinations ideally only take a few extra

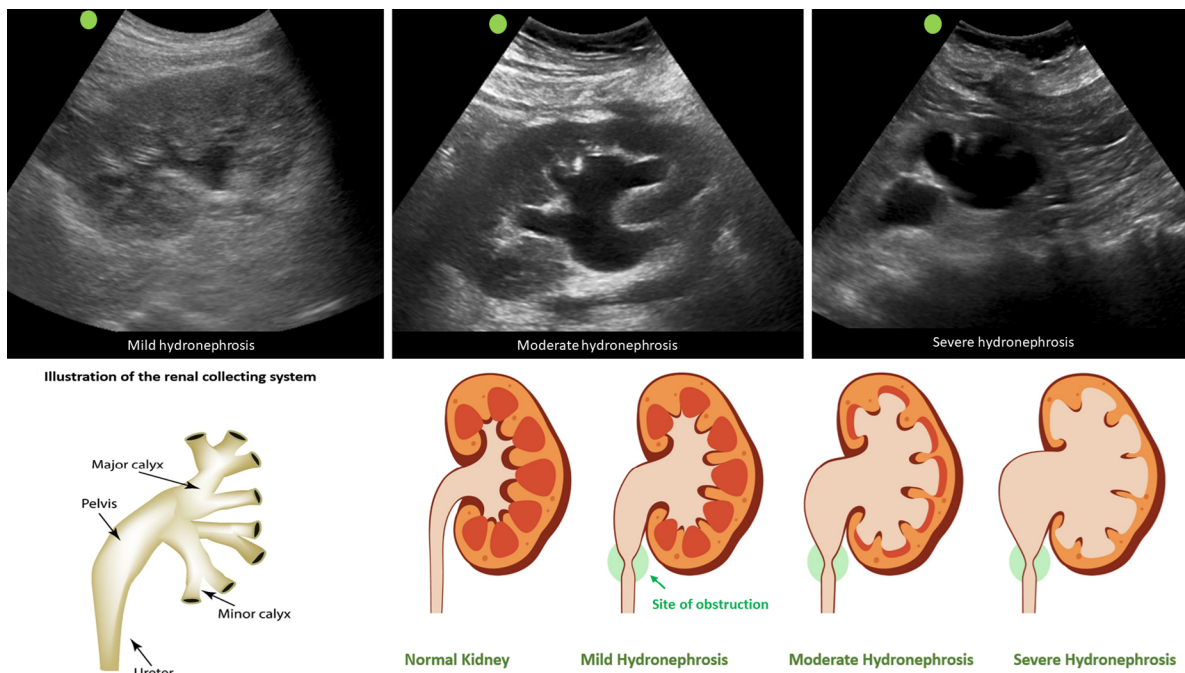


Figure 7 Sonographic appearance of hydronephrosis and its qualitative grading. Hydronephrosis appears as an anechoic (black) branching structure representing dilated collecting system. Citation: Koratala A. The Ultrasound Mimics of Hydronephrosis. Renal Fellow Network. [cited 18 June 2023]. Available from: <https://www.renalfellow.org/2019/05/10/the-ultrasound-mimics-of-hydronephrosis/#:~:text=Prominent%20renal%20vasculature%20and%20vascular,also%20appears%20black%20on%20ultrasound>. Copyright© 2019. Published by Renal Fellow Network (corresponding author's prior open access publication).

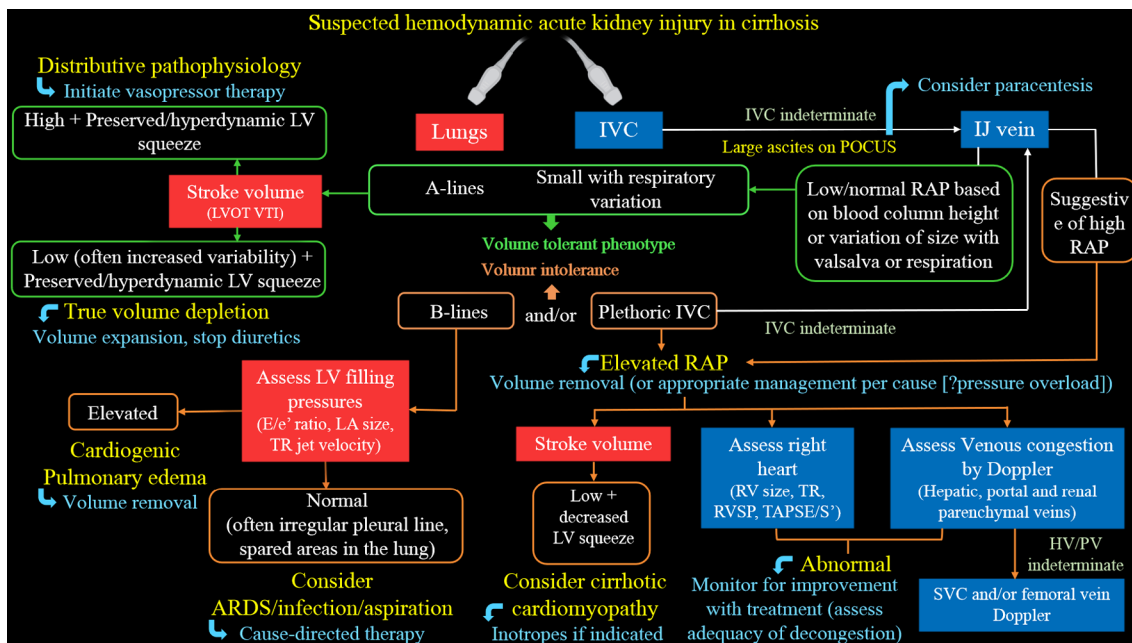


Figure 8 Proposed diagnostic algorithm for approaching acute kidney injury in a patient with cirrhosis. Citation: Koratala A, Reisinger N. Point of Care Ultrasound in Cirrhosis-Associated Acute Kidney Injury: Beyond Inferior Vena Cava. *Kidney360* 2022; 3: 1965-1968. Copyright© 2022 by the American Society of Nephrology (corresponding author's prior open access publication).

minutes, the cumulative time burden for physicians with heavy patient loads should be considered. Another priority is the development of practical POCUS protocols tailored to specific areas of clinical need, such as the evaluation of hyponatremia, hepatorenal syndrome, and cardiorenal syndrome. For example, Figure 8 presents a sample protocol outlining the evaluation of patients with hepatorenal dysfunction using the aforementioned sonographic applications [55]. This protocol serves as a visual guide, illustrating the step-by-step approach for utilizing POCUS in guiding management of these patients. Finally, it is important to acknowledge that performing POCUS without proper training or overestimating one's skills, as well as the capabilities of the equipment, can potentially lead to misdiagnosis and patient

harm.

FOOTNOTES

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Role of simulation in kidney stone disease: A systematic review of literature trends in the 26 years

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Abstract

BACKGROUND

Minimally invasive techniques for treatment of urinary stones requires expertise, experience and endoscopic skills. Simulators provide a low-stress and low-risk environment while providing a realistic set-up and training opportunities.

AIM

To report the publication trend of 'simulation in urolithiasis' over the last 26 years.

METHODS

Research of all published papers on "Simulation in Urolithiasis" was performed through PubMed database over the last 26 years, from January 1997 to December 2022. Papers were labelled and divided in three subgroups: (1) Training papers; (2) Clinical simulation application or surgical procedures; and (3) Diagnostic radiology simulation. Each subgroup was then divided into two 13-year time periods to compare and identify the contrast of different decades: period-1 (1997-2009) and period-2 (2010-2022).

RESULTS

A total of 168 articles published on the application of simulation in urolithiasis over the last 26 years (training: $n = 94$, surgical procedures: $n = 66$, and radiology:

$n = 8$). The overall number of papers published in simulation in urolithiasis was 35 in Period-1 and 129 in Period-2, an increase of +269% ($P = 0.0002$). Each subgroup shows a growing trend of publications from Period-1 to Period-2: training papers +279% ($P = 0.001$), surgical simulations +264% ($P = 0.0180$) and radiological simulations +200% ($P = 0.2105$).

CONCLUSION

In the last decades there has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs. With the development of 3D-printed and high-fidelity models, simulation for surgical procedure planning and patients counseling is also a growing field and this trend will continue to rise in the next few years.

Key Words: Kidney calculi; Urolithiasis; Simulation; Ureteroscopy; Percutaneous nephrolithotomy; Artificial intelligence

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Core Tip: The role of simulation training in the management of kidney stones has evolved. There has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs. With the development of three-dimensional printed and high-fidelity models, simulation for kidney stone procedure planning and patients counseling is also a growing field and this trend will continue to rise in the next few years.

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INTRODUCTION

Minimally invasive techniques for treatment of urinary stones require expertise, experience and endoscopic skills[1]. The learning curve to gain precision and accuracy in endoscopic procedures such as ureteroscopy (URS) and percutaneous nephrolithotomy (PCNL), and shockwave lithotripsy (SWL), has proven to be steep, leading to the need for training in non-operating settings[2]. Simulators provide a low-stress and low-risk environment while providing a realistic set-up and training opportunities and example of endoscopic procedures[3].

Different types of simulators can be found in the literature, with various degrees of fidelity or realism, and varying in costs[4]. Benchtop simulators are inanimate models that come cheap and are widely available, reusable and portable. Being useful for mastering the use of endoscopic instruments, these models are yet not as realistic and seem to be more appropriate for novice surgeons[5]. Realistic ex-vivo models, for example animals or human cadavers would in fact be more appropriate for advanced training, who need to master more intricate steps and advanced procedures[6].

Animal and cadaver simulators have greater costs than inanimate devices, can only be used once, and can have ethical issues[7]. The most recently developed type of simulators is based on virtual reality (VR), a computer-based simulation model that can mimic basic procedures as well as advanced interventions, being realistic and able to instantly give feedback to the trainees[8]. VR is a reusable simulator with amazing applicability but has high purchase costs and unreliable haptics.

Numerous studies have been performed on application of simulators in training of residents and expert surgeons, with focus on costs, performance, learning curve and standardized protocols[9]. As gathered from data, simulators are increasingly relied on for urology resident training worldwide[10].

Nonetheless, VR simulators, benchtop and three-dimensional (3D) printed models are now being used as tools to improve performance of endoscopic procedure in a patient-specific settings[11], for example developing a case-specific surgical planning before entering the operation theatre or simulating outcomes of different approaches. In particular, several studies reported the application for preoperative simulated puncture in complex PCNL, on different simulator models[12]. Moreover, simulators can be used to study performance and comparison of different instruments as laser fibers and their settings, endoscopic baskets or flexible scopes, without risking endangering patients in an in-vivo surgical procedure[13].

As a tool for enhancing patient-surgeon relationship and counseling, simulators have even been used to improve patient understanding of the disease and surgical procedure, resulting in higher levels of postoperative satisfaction[14].

The increasing trend of application of artificial intelligence and its subsets in the management of urolithiasis has already been investigated, with promising results[15]. It appears that the application of simulators is spreading in the urologic scientific community, from training to research and surgical planning. In this comprehensive review, we aim to report the publication trend of 'simulation in urolithiasis' over the last 26 years.

MATERIALS AND METHODS

Research of all published papers on “Simulation in Urolithiasis” was performed through PubMed database over the last 26 years, from January 1997 to Dec 2022, using MeSH terms, title words, and key words (Figure 1).

Search strategy and study selection

Cochrane methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to shape the study design[16]. All papers with relevant abstracts were identified through search on online database PubMed from 1997 to 2022.

Keywords used for searching included: “Urolithiasis”, “Kidney calculi” and “Stones”. MESH terms used in this screening process were: “Simulation”, “Virtual Reality”, “Augmented Reality”, “Mixed Reality”, “URS Simulation”, “PCNL Simulation”, “SWL Simulation”, “3D printing”, “Training”, “Training box”, “Bench Training”, “Phantom” and “Bench model”. All English and non-English abstracts were screened as there was no language restriction in the study. Systematic and non-systematic reviews were included in the study. Studies without a published abstract were excluded, as well as animal studies, human cadaveric studies and case reports.

After screening and extraction, papers were label according to subject: Training papers, studies on clinical applications or surgical procedures (surgical: URS, PCNL, SWL; instruments performance: Ureteral stent, scope, lithotripter, laser), studies of diagnostic (radiology) simulation on phantoms.

To better analyze the trend variation, papers were divided according to time of publication into two time periods: Period-1 (1997-2009) and Period-2 (2010-2022).

Evidence acquisition: criteria for including studies for this review

Inclusion criteria: All English language studies with a published abstract; All non-English studies with abstracts published in the English language; Studies reporting on simulation in urolithiasis: Training simulations with box simulators, phantoms for both diagnostic and therapeutic procedures; Simulations device for surgical planning (URS, PCNL, SWL) and patient-specific simulation; Studies of surgical performance using simulators (scopes, ureteral stents, laser fibers, lithotripters).

Exclusion criteria: Studies without a published abstract; Studies for non-urolithiasis conditions; Studies on human cadavers or animals; Case reports and meeting abstracts.

Two authors (C.N., V.J.) independently performed a literature search to identify studies and discrepancies were resolved after input and discussion with the senior author (B.K.S). Extracted articles on simulation were then divided in three subgroups according to field of interest: (1) Training; (2) Clinical application; and (3) Radiology simulation (Figure 2). Each subgroup was then divided into two 13-year time periods to compare and identify the contrast of different decades: Period-1 (1997-2009) and Period-2 (2010-2022).

Data were collected using Microsoft Excel (version 2007), analyzed through the independent *t* test. A statistically significant threshold level was stated at $P < 0.05$ to rule out possible difference in the data collected from Period-1 *vs* Period-2.

RESULTS

Overall number of papers

A total of 168 articles published on the application of simulation in urolithiasis over the last 26 years (training: $n = 94$, surgical procedures: $n = 66$, and radiology: $n = 8$). 164 papers were published in English; only 4 articles had an English language abstract and a non-English full paper: 1 in Chinese, 1 in French, and 2 in Russian.

For training procedures, articles included URS training ($n = 53$), PCNL training ($n = 22$) or simulation training for both these procedures ($n = 19$). Clinical application of simulation in surgical procedures included articles on URS ($n = 29$), PCNL ($n = 26$), SWL ($n = 5$) and ureteral stenting ($n = 6$). Regarding radiological simulations with phantoms, articles were found with application on diagnostic procedures ($n = 5$) and intraoperative imaging features ($n = 3$).

The overall number of papers published in simulation in urolithiasis was 35 in Period-1 and 129 in Period-2, with a significant increase of +269% ($P = 0.0002$). Each subgroup shows a growing trend of publications from Period-1 to Period-2: training papers +279% ($P = 0.001$), surgical simulations +264% ($P = 0.0180$) and radiological simulations +200% ($P = 0.2105$).

Training simulation papers

Of the 94 papers on simulation for training in endourology, 72 were published in Period-2, accounting for more than 76% of current publications.

Analysis of application of simulators for URS ($n = 51$) shows a significant rise by +225% ($P = 0.0016$) in Period-2. Similarly, simulation papers on PCNL training ($n = 21$) had a steep increase of +850% ($P = 0.0023$) in Period-2. Looking at simulations with a mixed setting with both URS and PCNL procedures, the rise by +180% was not statistically significant ($P = 0.1275$). In this research, 11 reviews were found, with great interest in residents’ training with simulators, assessing learning curves and developing standardized protocols of training. In the last 5 years, from 2018 to 2022, the numbers of papers on training with simulation for URS, PCNL and mixed endourological training were 17, 11 and 10 papers respectively.

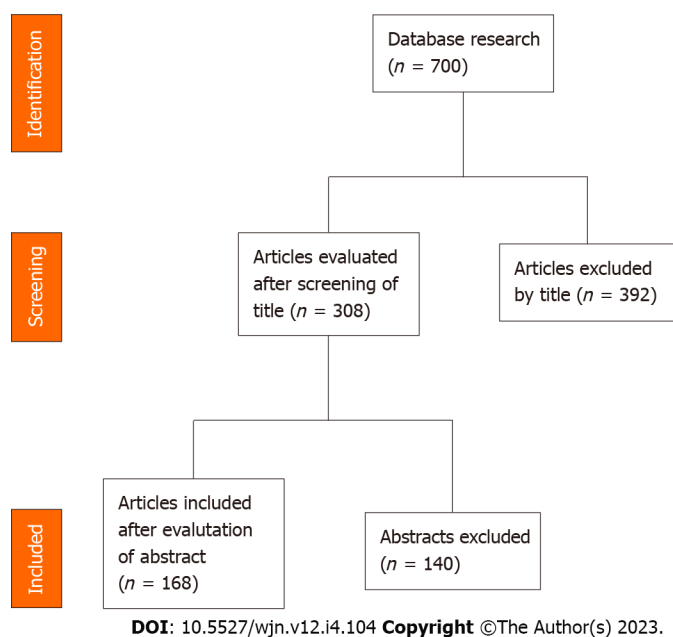


Figure 1 PRISMA flowchart of the included studies.

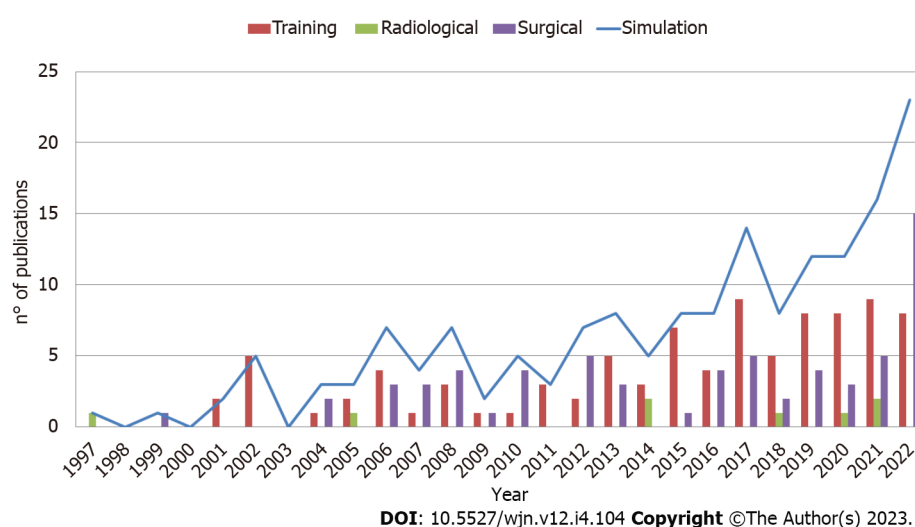


Figure 2 Trend of publications on 'Simulation in Urolithiasis' (trend line), with different subgroup as Training, Surgical and Radiological simulation.

Surgical simulation papers

Publication trend on surgical application of simulators in endourology has increased significantly ($P = 0.0180$) from Period-1 to period-2 (+264%), with 14 and 51 papers respectively.

Analysis of those papers found varied topics from application of patient-specific simulators (benchtop, 3D printed models, VR simulators) for surgical planning both in URS and PCNL, simulators of SWL (phantoms, VR) for predicting performance of lithotripsy, analysis of stent features in 3D models, evaluation of procedural instrumentation such as scopes, lasers, lithotripters and endoscopic baskets during surgical procedures (URS and PCNL).

Papers on simulations in URS ($n = 28$) rose significantly in Period-2 (+360%, $P = 0.0039$), PCNL simulations ($n = 26$) increased too (+1100%, $P = 0.0181$). SWL simulation and ureteral stent simulation on the other had reduced in period-2 (-33%, $P = 0.6983$ and -50%, $P = 0.5912$ respectively).

Radiological simulation papers

Application of simulators in radiology differed in our results from a diagnostic setting (preoperative), with phantoms used as tools to test efficiency of examinations, to a surgical setting (intraoperative), assessing quality of imaging and reconstructions. These increased from period-1 ($n = 2$) to period-2 ($n = 6$), a rise by +200% ($P = 0.2105$).

DISCUSSION

The role of simulation devices has been widely analyzed in the last decades, with particular attention to its application for training and assessment. Different studies have been proposed to rule out the efficacy in teaching residents' surgical skills in a non-operative setting, mostly with the aim to improve patient safety and reduce harm, while allowing a safe pre-surgical exposure to trainees[17]. The possibility to experiment difficult steps of endoscopic procedure, surgery that requires high level of training and experience, has been in fact a blessing in disguise[18]. The role of simulation in easing the learning curve of trainees has been positively reported, as well as its impact in leading the residents through difficult procedures in a low-stress setting[19].

Protocolshave then been developed to standardize resident training in a more efficient way[20], proposing different steps of expertise and accuracy, sometimes even with the aid of different simulators based on their grade of fidelity and accuracy[21].

What emerges from literature is that simulation can play a game-changing role in training. Its applications are almost infinite, ranging from easier procedure such as cystoscopic examination[22] and ureteral stent insertion, through to gain accuracy with complex procedures such as flexible URS and PCNL. Some models have even been developed to simulate unexpected scenarios like ureteral strictures, kinking and complications[23]. This allows trainees to get experience in more advanced scenarios without putting patients at risk.

Not every aspect of simulator training is perfect and even the more modern and technological simulators (VR for example) often lack enough realistic sensibility to train the haptics, and the absence of stress in a simulated environment can be misleading in the training process and may not allow trainees to deal with unexpected events[24].

There is an increasing trend of the use of simulators and simulation training over the last decade, and it is difficult to ignore the leading role simulators are playing in surgical improvement[10]. Our research found numerous papers on the application of simulation devices, especially phantoms and 3D printed models, for testing new technological devices.

In the studies regarding URS, laser fibers were tested to understand the effect different settings had on the stones or soft tissue, comparing different baskets and smaller scopes[25]. In PCNL simulation, the main focus emerged in the planning of renal puncture with accuracy and without perforation of neighboring structures[26]. To this aim, several studies have been performed in a patient-specific setting with realistic 3D-printed models[27]. As this review found out, the role of SWL in stone treatment has become progressively confined with only few papers found on application of simulation for SWL, for example analyzing gel properties or stone disruption, and none of them has been published in the last 10 years[28].

Development of 3D-printed models and VR has also been used in literature as an aid to counsel patients. Anatomically accurate models can influence the understanding of a patient's own disease, along with the surgical procedure, the possible complications and outcomes[29]. Recent studies have in fact pointed out the positive correlation that lies between the use of simulators in patient counseling and their overall satisfaction, with a positive role on surgeon-patient relationship and for avoiding misunderstandings[30]. This relatively new application of simulation could gain an important role in daily clinical practice.

Simulation based curriculum is now endorsed by the European Association of Urology (EAU) and European School of Urology (ESU)[31]. Other educational articles will help reinforce the training perspective to trainees[32]. There also seems to be an increasing role of artificial intelligence for training and education[33].

Strengths and weakness of bibliometric trend analysis

In this review, the first to our knowledge to evaluate the trend of publication of simulation in urolithiasis over the last 26 years, we aimed to report a comprehensive scenario of current literature. Both English and non-English language studies have been included in this review. On the other hand, the authors are aware that limiting our research to PubMed database, some articles published in non-index journals might have been missed. We consider though this to be a minor limitation, as bibliographic accuracy should still be obtained from this database alone[34]. This review is intended to analyze publication trends on simulation in the management of urolithiasis, and it does not just include training or clinical papers[35,36], but all studies performed with the application of simulators in endourology.

CONCLUSION

This review found an increasing bibliometric publication trend on the application of simulators in endourological practice. In the last decades there has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs. With the development of 3D-printed and high-fidelity models, simulation for surgical procedure planning and patients counseling is also a growing field and this trend will continue to rise in the next few years.

ARTICLE HIGHLIGHTS

Research background

Minimally invasive techniques for treatment of urinary stones requires expertise, experience and endoscopic skills. Simulators provide a low-stress and low-risk environment while providing a realistic set-up and training opportunities.

Research motivation

To report the publication trend of 'simulation in urolithiasis' over the last 26 years.

Research objectives

To analyze the simulation trends over the last 26 years.

Research methods

Research of all published papers on "Simulation in Urolithiasis" over the last 26 years: (1) Training papers; (2) Clinical simulation application or surgical procedures; and (3) Diagnostic radiology simulation. Data was further analyzed in two 13-year time periods to compare and identify the contrast of different decades: Period-1 (1997-2009) and period-2 (2010-2022).

Research results

A total of 168 articles published on the application of simulation in urolithiasis over the last 26 years (training: $n = 94$, surgical procedures: $n = 66$, and radiology: $n = 8$). The overall number of papers published in simulation in urolithiasis increased over time for all three areas with more simulation based studies in the last decade.

Research conclusions

In the last decades there has been a step up of papers regarding training protocols with the aid of various simulation devices, with simulators now a part of training programs.

Research perspectives

Simulation trends could guide future researchers on training and safe surgical practice patterns.

FOOTNOTES

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Seeing through the myths: Practical aspects of diagnostic point-of-care ultrasound in nephrology

Abhilash Koratala, Amir Kazory

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Abstract

Point of care ultrasonography (POCUS) is emerging as an invaluable tool for guiding patient care at the bedside, providing real-time diagnostic information to clinicians. Today, POCUS is recognized as the fifth pillar of bedside clinical examination, alongside inspection, palpation, percussion, and auscultation. In spite of growing interest, the adoption of diagnostic POCUS in nephrology remains limited, and comprehensive training beyond kidney ultrasound is offered in only a few fellowship programs. Moreover, several misconceptions and barriers surround the integration of POCUS into day-to-day nephrology practice. These include myths about its scope, utility, impact on patient outcomes and legal implications. In this minireview, we address some of these issues to encourage wider and proper utilization of POCUS.

Key Words: Ultrasound; Point of care ultrasonography; Doppler; Congestion; Hemodynamics; Nephrology

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Core Tip: Nephrologists frequently encounter challenges in assessing fluid volume status in their daily practice, and point of care ultrasonography (POCUS) can significantly enhance the sensitivity of traditional physical examination in such scenarios. Not only does POCUS aid in swift diagnosis, but it also reduces fragmentation of care. While it may obviate the need for additional imaging studies in specific cases, it should not be considered a replacement for comprehensive consultative imaging. The effectiveness of POCUS largely relies on the proficiency and experience of the operator, which, in turn, is influenced by the quality of training provided.

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INTRODUCTION

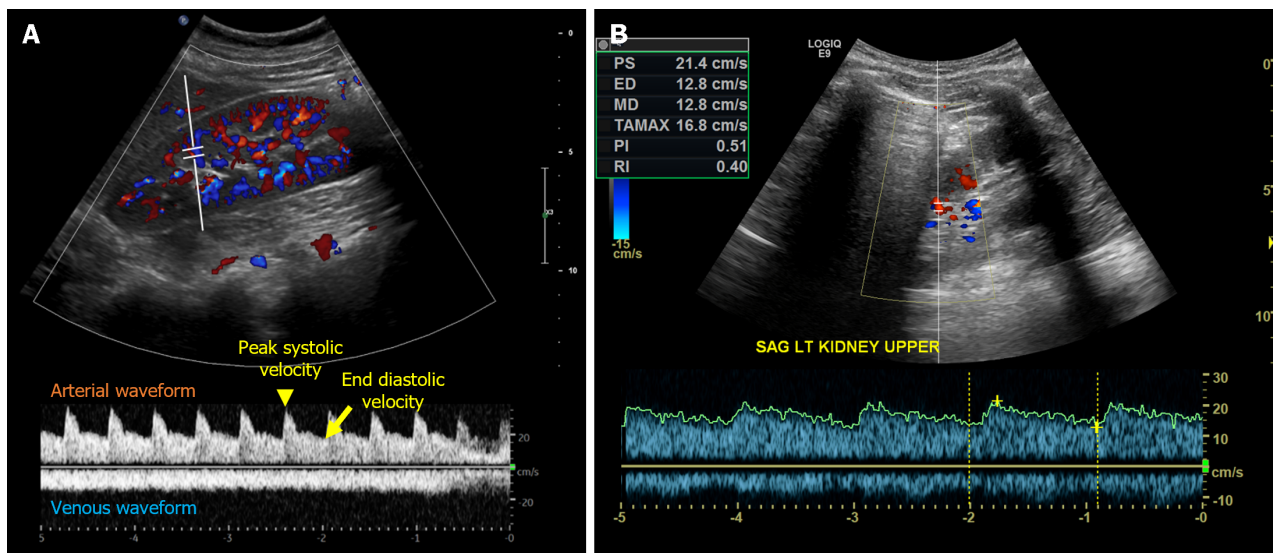
Point of care ultrasonography (POCUS) is a focused ultrasound examination performed by the treating clinician at the bedside to address specific questions that aid in guiding patient management[1]. Ultrasonography itself has been a trusted imaging modality for several decades. During the 1980s, the development of real-time ultrasound revolutionized the way sonographic images were viewed, eliminating any lag between signal generation and image display. This breakthrough created new opportunities for physicians to perform bedside ultrasound evaluations of trauma patients in emergency settings, leading to the evolution of the POCUS we recognize today[2]. With ongoing technological advancements and the miniaturization of ultrasound devices, POCUS has gained significant momentum in the recent past emerging as the fifth pillar of physical examination alongside traditional four pillars, namely inspection, palpation, percussion, and auscultation. As such, it is being incorporated into medical school curricula. According to a 2019 survey, over 70% of the responding medical schools in the United States reported having a formal POCUS curriculum. Interestingly, 73.8% of these schools have integrated POCUS into basic science courses, highlighting its role in establishing a strong foundation in anatomy and physiology before entering the clinical years[3]. Despite growing interest, the adoption of diagnostic POCUS in nephrology remains sparse and comprehensive training beyond kidney ultrasound is only offered by a few select fellowship programs[4]. This has two significant implications for the near future. Firstly, prospective nephrology fellows who already received basic POCUS training and anticipate learning specialty-specific POCUS applications during their fellowship are left disappointed. This negatively impacts the already dwindling interest in nephrology as a career choice. Secondly, when fellows with some POCUS training use it during rounds, it can create confusion in the clinical decision-making process if the supervising physicians are unfamiliar with the findings. In addition to the lack of trained faculty, several misconceptions surrounding the use of POCUS hinder its widespread adoption. In this minireview, we aim to dispel common myths associated with integrating POCUS into day-to-day nephrology practice.

Myth: Pocus is the same as a comprehensive ultrasound study performed by the radiology department

POCUS constitutes limited ultrasound examinations performed by the clinician at the patient's bedside, with the specific purpose of answering "focused questions" to confirm a suspected diagnosis or narrow down the differential. Examples of such questions include, "Does this patient with acute kidney injury (AKI) have hydronephrosis?", "Does this patient with intra-dialytic hypotension have pericardial effusion?", or "Is this location of arteriovenous fistula suitable for cannulation?". On the other hand, comprehensive referral ultrasound studies performed by the radiology or cardiology departments involve a thorough assessment of an anatomical region, documenting predefined parameters and measurements. In addition, POCUS reduces fragmentation of care by allowing multiple evaluations performed during the same study. For example, a nephrologist evaluating a patient with suspected congestive nephropathy can assess cardiac function, right atrial pressure, presence or absence of venous congestion, pleural effusion, and ascites in a few minutes at bedside[5,6]. In contrast, without POCUS, obtaining answers to the same questions would require ordering a multitude of studies, including an echocardiogram, a chest radiograph, an abdominal sonogram, and a duplex study of the right upper quadrant and kidney. This process would consume significant time and resources, more so when repeating an entire study to follow one or two imaging parameters (*e.g.*, improvement in Doppler stigmata of venous congestion). With that being said, POCUS users need to use their clinical judgement in order to decide when a focused examination would suffice and when a more extensive assessment may be necessary to make accurate and informed clinical decisions. For instance, while a nephrologist using POCUS might be able to detect mitral regurgitation as a potential cause for unilateral pulmonary edema, accurately grading the lesion and providing detailed information related to mitral valve surgery would be beyond their expertise. Likewise, while a POCUS user may suspect renal artery stenosis based on the intrarenal Doppler waveform, performing a comprehensive evaluation would be time-consuming and necessitates skill levels beyond typical POCUS training (Figure 1).

Myth: Pocus is unnecessary if we improve training in conventional physical examination skills

It is true that physical examination skills are declining among physicians[7,8]. However, a less acknowledged aspect is that the diagnostic accuracy of physical examination is limited[9-12]. The so-called 'classic' signs and symptoms were described in an era when late-stage presentations were common, often occurring after the onset of significant symptoms. As a result, there is a need for a more sensitive bedside tool to detect pathology earlier, before substantial organ damage has occurred, and to provide timely guidance for patient management. Therefore, it is essential not only to enhance the instruction of physical examination skills but also to augment them by incorporating POCUS. It is now well-established that POCUS significantly improves the sensitivity of physical examination. For instance, in a study including 32 patients with acute respiratory distress syndrome, lung ultrasound demonstrated a diagnostic accuracy of 93% for pleural effusion, 97% for alveolar consolidation, and 95% for alveolar-interstitial syndrome. In comparison, the accuracy of auscultation in detecting these abnormalities was much lower, at 61%, 36%, and 55%, respectively[13]. Similarly, in a study involving 926 critically ill patients admitted to the intensive care unit, it was observed that 51% of those with



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Figure 1 Intrarenal Doppler. A and B: Intrarenal Doppler demonstrated normal waveforms (A), tardus parvus (B) waveform in a case of suspected renal artery stenosis that should warrant further investigations such as radiology-performed Doppler ultrasonography and/or magnetic resonance angiography. A and B: Citation: Batool A, Chaudhry S, Koratala A. Transcending boundaries: Unleashing the potential of multi-organ point-of-care ultrasound in acute kidney injury. *World J Nephrol* 2023; 12: 93-103. Copyright© The Authors 2023. Published by Baishideng Publishing Group Inc (corresponding author's prior open access publication).

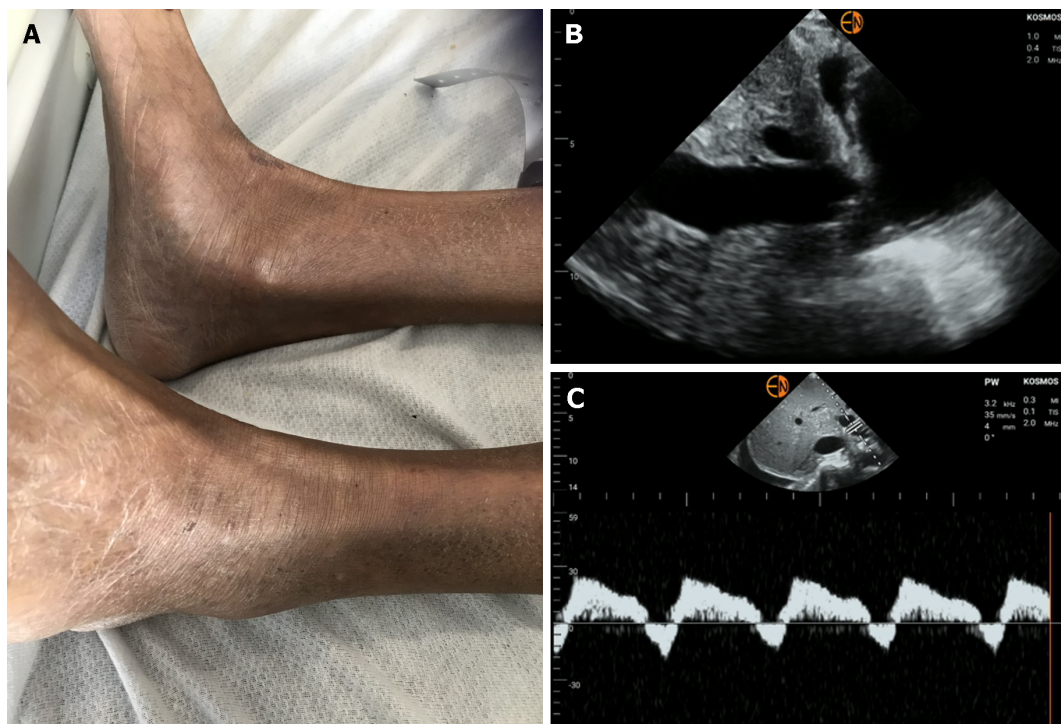
pulmonary edema on lung POCUS showed normal findings on auscultation[14]. Moreover, the incorporation of POCUS has demonstrated significant improvements in diagnostic capabilities for common cardiac conditions[15-17]. These observations are very much relevant to nephrologists who frequently rely on physical examination to assess volume status and adjust ultrafiltration goals or diuretic therapy. Furthermore, certain applications such as ruling out obstructive uropathy or evaluating venous blood flow patterns to guide decongestive therapy, cannot be achieved through conventional examination methods regardless of clinicians' skill level. **Figure 2** depicts a scenario in which a patient with heart failure and AKI received intravenous fluids under the assumption of overdiuresis, given the absence of pedal edema or shortness of breath. Nevertheless, POCUS revealed a dilated inferior vena cava and significantly pulsatile portal vein, indicating severe venous congestion. In response to these findings, intravenous diuretics were administered, leading to an improvement in serum creatinine levels.

Myth: The scope of nephrologist-performed pocus is confined to kidney ultrasound

The scope of POCUS depends on two main factors: Physician's competency and the relevance of a specific sonographic application to the physician's specialty. There is little debate about the relevance of kidney and urinary bladder ultrasound for nephrologists, as they are expected to diagnose structural abnormalities of the kidneys and integrate this information into clinical decision-making[18]. However, in real-life situations, consulting teams often order a formal renal sonogram before seeking nephrology input in cases of AKI. Therefore, while nephrologist-performed urinary tract POCUS can be beneficial, its utility is limited to specific scenarios, such as avoiding patients' referral to radiology to get an ultrasound in the outpatient setting or diagnosing Foley catheter obstruction in a patient with sudden decrease in urine output, among others. A significant portion of a nephrologist's time on a consultation service is devoted to managing patients with complex fluid and electrolyte disorders. Therefore, it is conceivable that the assessment of volume status using POCUS is vital in nephrology practice. As outlined in prior publications, incorporating multi-organ POCUS, which includes focused cardiac ultrasound, lung ultrasound, and Doppler assessment of systemic veins, greatly assists in evaluating cases of hemodynamic AKI[5,19,20]. This is especially valuable in addressing common diagnostic challenges such as hepatorenal dysfunction[21]. In addition, POCUS facilitates assessment of acute abnormalities of arteriovenous access in the dialysis unit and thereby guides appropriate management. **Figure 3** outlines the sonographic applications commonly used in nephrology practice. The next question is whether nephrologists are permitted to perform multi-organ POCUS. The answer is yes. In 1999, the American Medical Association House of Delegates passed a resolution (H-230.960; reaffirmed 2020) stating that "ultrasound imaging is within the scope of practice of appropriately trained physicians"[22]. Additionally, each hospital's medical staff should review and approve criteria for granting ultrasound privileges, taking into account physicians' background and training in accordance with recommendations developed by their respective specialty societies. Hence it is clear that the ability to perform POCUS is not determined by the physician's specialty but rather by their training and competency. Currently, nephrologists have access to multiple certification opportunities tailored to their skill levels though development of specialty-specific universal competency standards remains a work in progress[23].

Myth: Pocus should be incorporated only if it enhances patient survival

POCUS is often criticized for the lack of robust data demonstrating its direct impact on mortality. However, it is essential



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Figure 2 A case of discrepant clinical and point of care ultrasonography findings. A: Absent pedal edema; B: Plethoric inferior vena cava suggestive of elevated right atrial pressure; C: Pulsatile portal vein Doppler with flow reversal indicative of severe venous congestion.

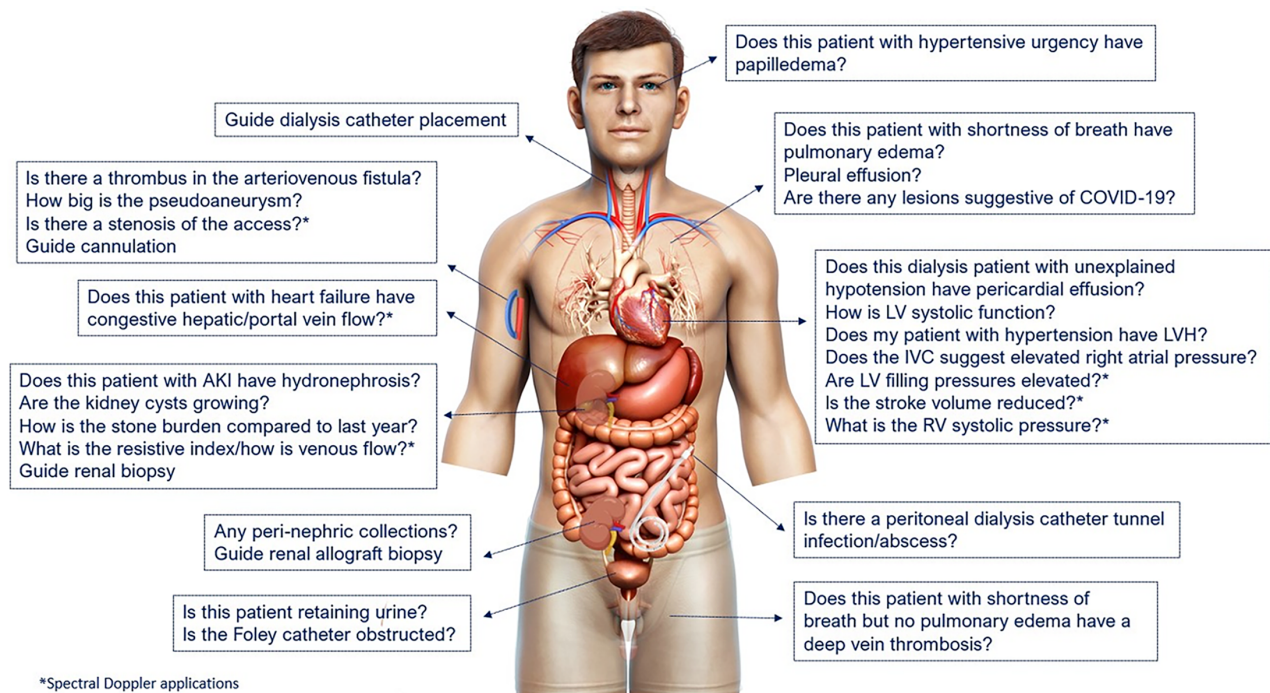


Figure 3 Scope of nephrology-related point of care ultrasonography: Organ-specific focused questions that can be answered by bedside ultrasonography. Those marked with asterisk (*) indicate advanced sonographic applications requiring a higher operator skill level/additional training. COVID-19: Coronavirus disease 2019; LV: Left ventricle; LVH: Left ventricular hypertrophy; IVC: Inferior vena cava; RV: Right ventricle. 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. The authors have obtained the permission for figure using from the Wolters Kluwer Health, Inc (Supplementary material).

to remember that POCUS is a diagnostic aid. For a meaningful effect on mortality, it needs to be combined with treatments that have the ability to improve patient survival. As a diagnostic test, POCUS is expected to have better diagnostic accuracy compared to conventional methods, which it does as discussed above. Nevertheless, POCUS findings do have a significant impact on several clinically relevant and measurable outcomes such as time to diagnosis, need for imaging studies, healthcare cost burden, and patient satisfaction. For instance, in a systematic review and meta-analysis including 5393 patients with dyspnea, the time to correct diagnosis and treatment were significantly shorter in the POCUS group compared to those receiving conventional care (mean difference -63 min and -27 min respectively). Interestingly, patients in the POCUS group had significantly higher odds of receiving appropriate therapy *vs* controls (odds ratio = 2.31; 95% confidence interval: 1.61-3.32). Further, the length of stay in the intensive care unit was significantly shorter in the group managed using POCUS (mean difference -1.27 d)[24]. This clinical scenario is pertinent to nephrologists as they are often responsible for managing patients with dyspnea related to fluid overload. The ability to quickly differentiate between dyspnea caused by fluid accumulation and other potential causes is crucial in guiding appropriate interventions. Similarly, POCUS-guided management has shown to reduce the number of subsequent imaging studies including chest radiographs, echocardiograms and computed tomography scans thereby having a favorable impact on the healthcare costs[25,26]. Likewise, in hemodialysis patients, POCUS-guided titration of ultrafiltration has demonstrated more significant reductions in left ventricular filling pressures, cardiac chamber dimensions and ambulatory blood pressure readings, indicating an effective treatment approach[27,28]. With respect to patient-reported outcomes, there is increasing evidence that POCUS enhances patient satisfaction and facilitates better understanding of their diagnosis[29,30]. This is of particular interest to nephrologists, as they must adeptly communicate dietary restrictions and medication adherence to asymptomatic patients. In this context, discussing and presenting POCUS images to patients could prove effective[31]. The fundamental responsibility of a physician is to make accurate diagnoses through thoughtful integration of history and physical examination findings. It is illogical to forgo the use of improved bedside diagnostic tools merely because there may not be a treatment that directly impacts mortality.

Myth: Acquiring competency in pocus is a fast and simple process

POCUS comprises three essential components: Image acquisition, interpretation, and clinical integration. Competency in POCUS means being proficient in all these aspects. In medical school, students typically receive longitudinal instruction in physical examination, starting from the first year, progressing from normal findings to abnormal findings, and finally, correlating these findings clinically to arrive at a diagnosis and develop a management plan. As such, it is logical to assume that achieving competency in POCUS cannot be accomplished just by attending a short course. It requires persistent practice under the guidance of experts, if possible, or at the very least, cross-checking findings with the reports of formal imaging studies till the learner is consistently able to obtain images of acceptable quality and independently interpret them. The duration of training can vary significantly based on the specific sonographic applications and the level of expertise needed. For instance, mastering Doppler echocardiography takes considerably more time compared to learning how to obtain basic cardiac views. As expected, the literature documents highly variable training durations, ranging from 4-320 h according to a systematic review[32]. Merely attending training sessions does not ensure competence. It must be assessed through various methods, such as knowledge checks, objective structured clinical examinations, standardized direct observation tools and periodic quality assessments. In addition, a benchmark of a minimum number of scans to be performed is commonly used when determining certification criteria or granting hospital privileges for POCUS. For example, the American College of Emergency Physicians policy statement on emergency ultrasound recommends that a trainee should perform a minimum of 25-50 quality-reviewed ultrasounds per core application and a total of 150-300 scans as part of POCUS training[33]. These recommendations are widely adopted by hospital credentialing committees and other POCUS-performing specialties albeit with necessary modifications depending on the scope of practice. In nephrology, current expert recommendation includes a minimum of 25 quality-reviewed scans per basic application (*e.g.*, kidney, focused cardiac, lung, vascular access) and 50 per advanced application (*e.g.*, Doppler cardiac, systemic venous Doppler, arteriovenous fistula flow assessment)[34]. To summarize, mastering POCUS is a gradual and long-term process, and physicians should plan for a stepwise learning approach. Additionally, it is crucial to be aware of both personal limitations and the limitations of the equipment being used (*e.g.*, handheld ultrasound device *vs* a traditional portable machine) when interpreting the scans to avoid misdiagnosis or missing significant findings. All these factors must be taken into consideration when nephrology faculty are considering starting a POCUS training program at their institutions. Division leadership should acknowledge the significant time commitment involved and allocate the necessary resources to support the initiative. Figure 4 depicts essential elements for implementing a robust POCUS program within an institution.

Myth: Pocus has limited utility because of its operator-dependent nature

POCUS is frequently criticized for its operator-dependent nature, but this limitation is intrinsic to ultrasonography as an imaging method in general irrespective of who performs it (*e.g.*, a nephrologist or a professional sonographer or a radiologist). In contrast to other imaging modalities such as CT or magnetic resonance imaging with standardized image acquisition, obtaining optimal images relies on the expertise of the person performing ultrasound. Therefore, it is not a POCUS-specific (clinician-performed ultrasound) limitation. In reality, nearly every aspect of physician-patient interaction, such as history-taking, physical examination, and interpreting laboratory data, is operator-dependent. The emphasis should be on providing proper training to the operator rather than blaming the modality itself.

Myth: Incorporating pocus makes physicians more susceptible to lawsuits

The fear of misinterpreting findings or overlooking incidental findings, which could lead to adverse legal actions, is

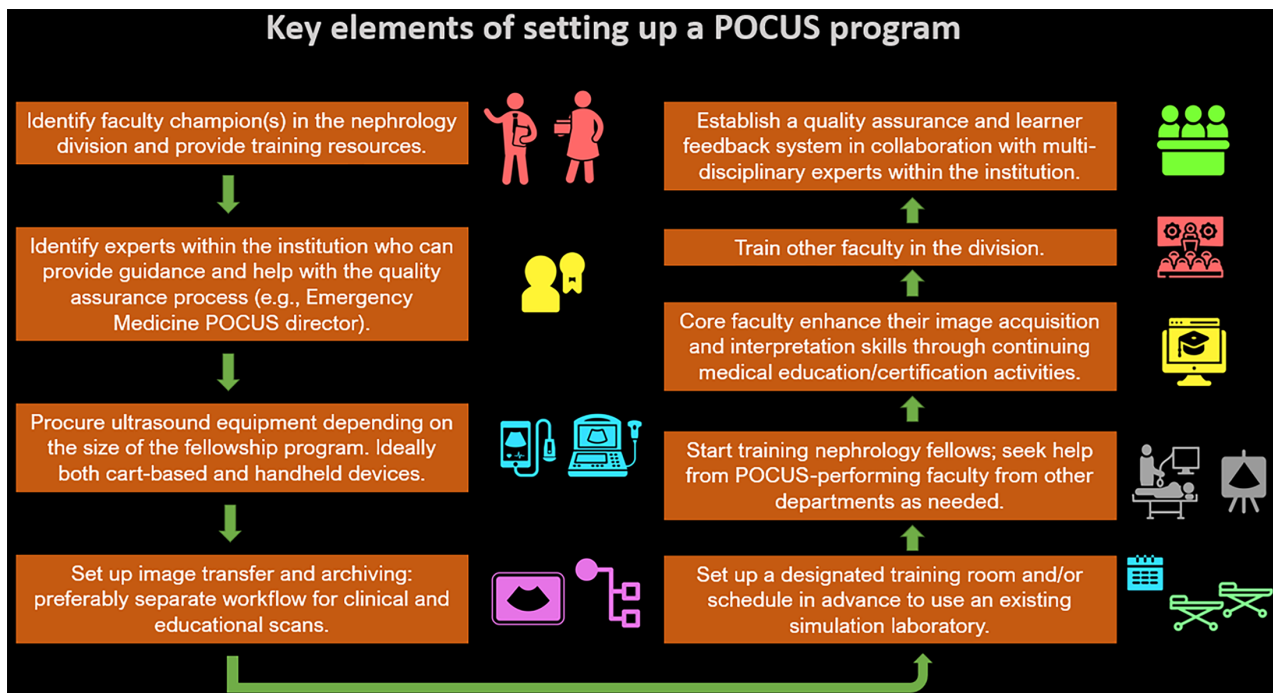


Figure 4 Flow chart depicting the key elements of establishing a point of care ultrasonography program at the institutional level. POCUS: Point of care ultrasonography. Citation: Koratala A, Reisinger N. POCUS for Nephrologists: Basic Principles and a General Approach. *Kidney360* 2021; 2: 1660-1668. Copyright © 2021 by the American Society of Nephrology. The authors have obtained the permission for figure using from the Wolters Kluwer Health, Inc (Supplementary material).

frequently seen as a hindrance to the adoption of POCUS in nephrology practice^[35]. Several studies have examined lawsuits involving POCUS performed by various specialties. However, to date, no study has indicated that missed findings on focused or limited ultrasound scans resulted in adverse legal action against physicians. Instead, the research suggests that adverse legal action is more commonly associated with failure to perform POCUS in a timely manner when required^[36-40]. In this context, implementing a hospital wide system for archiving POCUS images and standardizing the reporting of findings can be beneficial. Such a system streamlines the process of providing timely feedback to trainees, facilitates billing procedures, and allows for seeking expert opinion when uncertainty arises.

CONCLUSION

In conclusion, POCUS serves as a valuable addition to nephrologists' toolkit, enhancing bedside diagnosis. However, it is essential to remember that no matter how advanced the technology is, it cannot replace astute clinical judgment and the appropriate integration of clinical information. This rule applies to POCUS as well, because any oversight in attention to details, improper technique, or misinterpretation of findings may lead to inappropriate patient management. As such, professional organizations should collaborate in developing guidelines for training and accreditation processes. Future studies should focus on assessing the impact of structured longitudinal curricula on learners' competency and establishing protocols for the optimal use of POCUS in various nephrology-related clinical scenarios.

FOOTNOTES

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Cryptococcosis in kidney transplant recipients: Current understanding and practices

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Abstract

Cryptococcosis is the third most commonly occurring invasive fungal disease in solid organ transplant recipients (SOT). It is caused by encapsulated yeast, *Cryptococcus* species, predominantly *Cryptococcus neoformans* and *Cryptococcus gattii*. Though kidney transplant recipients are at the lowest risk of cryptococcosis when compared to other solid organ transplant recipients such as lung, liver or heart, still this opportunistic infection causes significant morbidity and mortality in this subset of patients. Mortality rates with cryptococcosis range from 10%-25%, while it can be as high as 50% in SOT recipients with central nervous system involvement. The main aim of diagnosis is to find out if there is any involvement of the central nervous system in disseminated disease or whether there is only localized pulmonary involvement as it has implications for both prognostication and treatment. Detection of cryptococcal antigen (CrAg) in cerebrospinal fluid or plasma is a highly recommended test as it is more sensitive and specific than India ink and fungal cultures. The CrAg lateral flow assay is the single point of care test that can rapidly detect cryptococcal polysaccharide capsule. Treatment of cryptococcosis is challenging in kidney transplant recipients. Apart from the reduction or optimization of immunosuppression, lipid formulations of amphotericin B are preferred as induction antifungal agents. Consolidation and maintenance are done with fluconazole; carefully monitoring

its interactions with calcineurin inhibitors. This review further discusses in depth the evolving developments in the epidemiology, pathogenesis, diagnostic assays, and management approach of cryptococcosis in kidney transplant recipients.

Key Words: Cryptococcosis; Kidney transplant recipients; Amphotericin B; Immunosuppression; Fluconazole

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Core Tip: Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients. As an opportunistic infection, it poses substantial morbidity and mortality in kidney transplant recipients. Mortality rates for cryptococcosis range from 10% to 25%. In immunocompromised patients, especially in cryptococcus-endemic areas, cryptococcosis must be suspected and diagnosed with a low threshold. Compared to India ink and fungal cultures, tests for the cryptococcal antigen detection in cerebrospinal fluid or plasma test are more sensitive and specific. The management of cryptococcosis poses considerable difficulties, mostly done with reduction or optimization of immunosuppression in addition to lipid formulations of amphotericin B and fluconazole.

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INTRODUCTION

With the advent of a successful kidney transplantation way back in 1954, we have been able to ensure good initial graft outcomes with potent immunosuppression. Though potent, these drugs have their own side effect profiles[1]. Amongst these side effects, the most profound is higher rates of infections. Fungal infections occur in 15%-42% of organ transplant recipients. However, newer antifungal drugs have ensured a decline in these rates, especially invasive candidate infection. Cryptococcal infections generally are seen in the late post-transplant period, the time when anti-fungal prophylaxis is stopped[2]. Majority of these infections are due to the reactivation of pre-existing latent infections. Mortality rates are variable ranging from 33%-40% and are highest in those with central nervous system involvement[3]. Calcineurin inhibitors interestingly have anti-fungal activity *in vitro*. Tacrolimus showed more promising antifungal activity compared to cyclosporin and that might be due to efflux pump inhibition which is not present in cyclosporin[4]. Mammalian target of rapamycin inhibitors like rapamycin, and everolimus exhibit *in vitro* antifungal activity[5,6]. This however may not be truly protective against fungal infection in the real world. Considering the high mortality and even higher morbidity, there is a growing need for easily available highly specific diagnostic modalities for early diagnosis and treatment initiation. In this manuscript, we highlight the disease burden, the latest identification tools and outcomes in renal allograft recipients with present-day immunosuppression and anti-fungal therapy.

MICROBIOLOGY OF CRYPTOCOCCUS

Cryptococcus is a genus of basidiomycetous fungi with more than thirty species commonly found in the environment. There are only two species commonly known to be pathogenic, *C. neoformans* and *C. gattii*. *C. neoformans* was first identified as human pathogen in the late 19th century but was recognized as a common human causative organism of human disease in late 1970s[7]. The pathogenic yeasts can be subclassified into four serotypes based upon capsular agglutination reactions and are designated A, B, C or D. From a clinical prospective it is reasonable to divide cryptococcus into two species complexes: *C. neoformans* (serotype A, D) and *C. gattii* (serotype B, C)[8]. Majority of cryptococcal infection (around 95%) are caused by *C. neoformans* serotype A where as only 4%-5% infections are caused by *C. neoformans* serotype D or *C. gattii* serotype B, C. *C. neoformans* is found throughout the world in association with birds excreta like pigeons, environmental scavengers like amoeba and in a variety of tree species. *C. gattii* is commonly associated with several species of trees in tropical and subtropical climates[9-11]. The life cycle of cryptococcus involves both asexual and sexual forms. The asexual form exists as haploid encapsulated yeast and reproduces by budding. The yeasts are the only form of cryptococcus that have isolated from human infections. The sexual form is observed only in the laboratory[12]. Cryptococcus causes infection following inhalation of aerosolized infectious particles like desiccated yeast cells and basidiospores through the respiratory tract. Cryptococcal infection is acquired from the environment and the spread of infection from person to person has not been documented except with transplanted tissue[7,13].

EPIDEMIOLOGY

Cryptococcosis is an important opportunistic infection that leads to significant morbidity and mortality in transplant recipients. In solid organ transplant (SOT) recipients, it is the third most commonly occurring invasive fungal infection (IFI) after candidiasis and aspergillosis[14]. Though one recent retrospective observational study from Northern India highlighted the recent rise in angio-invasive fungal infections like mucormycosis and aspergillosis. Cryptococcosis was the fourth most commonly reported infection in this study preceded by mucormycosis, aspergillosis and pneumocystis jiroveci[15].

Cryptococcosis accounts for 8-10% of the invasive fungal infections in SOT recipients[15]. Its overall incidence in various cohorts of SOT recipients ranges from 0.2% to 5% depending on the type of organ transplanted[14,16,17]. As per a recently published retrospective analysis of the cohort of patients after organ transplantation from three states of the United States, the incidence of cryptococcosis was 0.32% after kidney transplantation which was lower than both lung and liver transplant recipients[18]. Shenoy *et al*[19] in their recent retrospective analysis showed a very low incidence of 0.04%.

Cryptococcosis primarily occurs due to the reactivation of the latent infection in the post-transplant period[20]. Two decades back, it occurred primarily amongst patients with human immunodeficiency virus (HIV), but now the majority of infections occur in non-HIV population, particularly immunosuppressed SOT recipients (60%-70% of the total cases) [21]. This may be explained by the emergence of highly active antiretroviral therapy for the treatment of HIV, along with an increase in the number of patients undergoing transplantation and the use of immunosuppressants. Calcineurin inhibitors (CNI) can affect the extent of the disease. Patients receiving CNIs were less likely to have disseminated disease due to their *in vitro* antifungal properties by targeting fungal homologs of calcineurin[22]. Steroids and T cell-depleting induction agents (antithymocyte or alemtuzumab) are associated with an increased risk of cryptococcosis[23,24].

Cryptococcosis is a late-occurring invasive fungal infection (after 1 year). It has a longer (574 d) median time to onset from the date of transplant as compared to invasive candidiasis (103 d) and aspergillosis (184 d)[25]. Based on the organ transplanted, the median time to onset is earlier after lung (191 d), heart (195 d) and liver (200 d) as compared to kidney transplantation (616 d)[18].

Mortality rates with cryptococcosis range from 10%-25%, while it can be as high as 50 % in SOT recipients with cryptococcal meningitis[26].

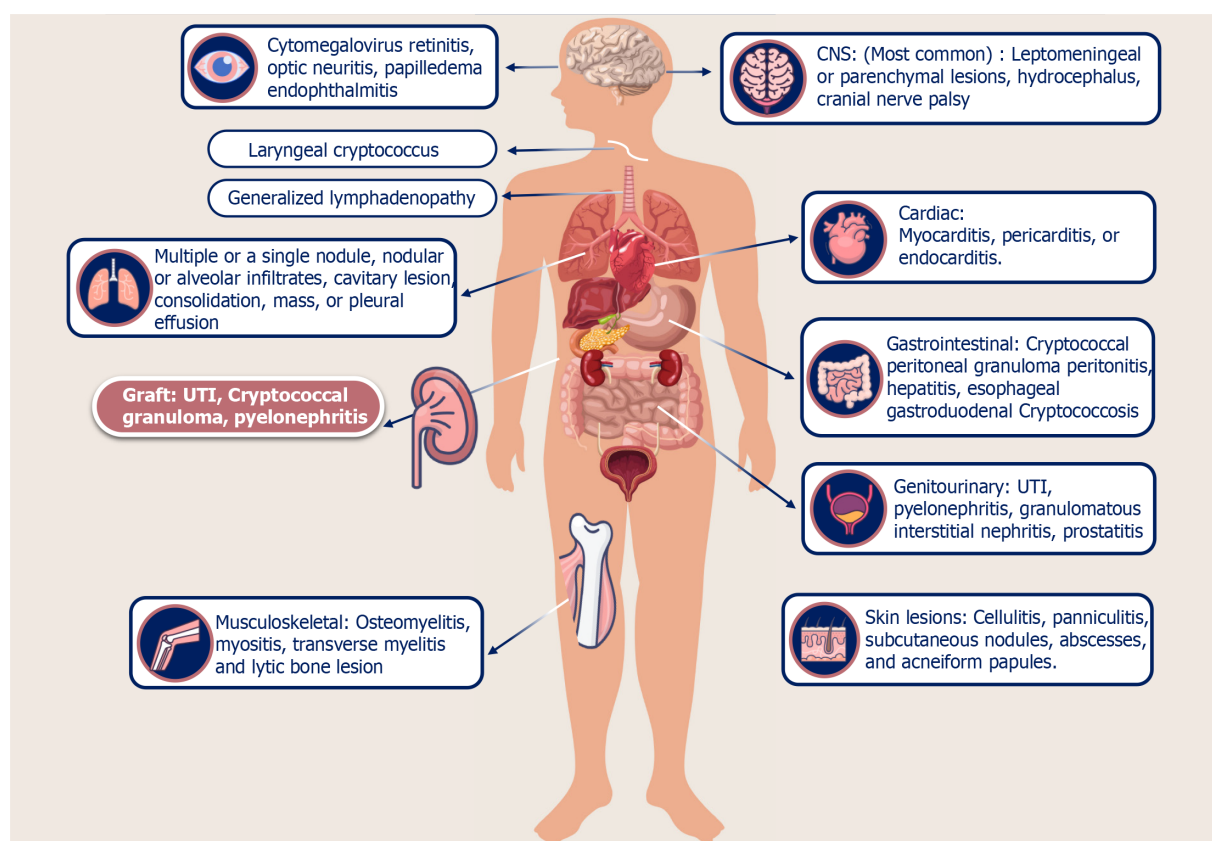
PATHOPHYSIOLOGY

C. neoformans is detected by a number of innate receptors, including Toll-like receptors, mannose receptors and -glucan receptors in the body during infection. Cells of innate immunity such as natural killer cells, dendritic cells, macrophages and neutrophils are primarily involved in *C. neoformans* killing in the host[27]. In particular, the establishment of Th1 and Th17 responses following the activation of macrophages is responsible for fungus clearance. Th1 and Th17 cells produce inflammatory cytokines such as IFN-, IL-17, and IL-22 in response to *C. neoformans* infection, resulting in robust antimicrobial and phagocytic responses[28]. Recently, studies have shown that mediators of death receptor-triggered extrinsic apoptosis, FADD and RIPK3 (immune regulators) control excessive inflammation during *C. neoformans* infection[29]. Replication of *C. neoformans* inside macrophages has been shown to be directly correlated with the susceptibility of the host to infection. Factors and conditions that modulate macrophage function causing T-cell function impairment such as in recipients of SOT can result in cryptococcal disease as a result of the reduced antifungal capacity of cells, facilitating the intracellular growth of *C. neoformans*[30]. *C. neoformans* releases an array of molecules such as prostaglandins and leukotrienes and virulence-associated enzymes that alter the local immune response of the host by having direct effects on inflammatory cells. Cryptococcal polysaccharides interfere with the migration of leukocytes toward chemoattractants[31]. The robust immune responses can at times be destructive to the organs of the host, especially to the lung parenchyma. Mouse models suggest CD4+ T cells mediates inflammation and host damage in the setting of *C. neoformans* infection[32]. Rarely, transmission can also occur from a donor allograft[33].

CLINICAL MANIFESTATION

Depending on the host's immunological condition, clinical signs of cryptococcal infection in a kidney transplant recipients (KTR) might range from asymptomatic colonization of the respiratory tract to wide dissemination[34]. The central nervous system (CNS) is the primary target site. *C. neoformans* is typically acquired through inhalation into the lungs, where it can spread to the skin, bone, myocardium, transplanted kidney and other organs. The cryptococcal infection in kidney transplant recipients might be the result of a recent acquisition or the recurrence of a latent or dormant infection. Epidemiological data has long suggested that cryptococcal infections exhibit dormancy and reactivation[22]. *Cryptococcus neoformans* possess the traits required for dormant infection in humans. In an analysis, of 52% of transplant recipients with cryptococcosis, there was evidence of a latent infection before the organ transplant[35]. **Figure 1** shows various organ involvement of the human body in cryptococcal infection.

Up to 70% of patients with cryptococcal illness have involvement of the central nervous system. Leptomeningeal or parenchymal lesions, as well as hydrocephalus, can be seen. Frequent clinical signs of CNS involvement include fever, headache, altered mental status, vomiting, seizure, and visual and auditory complaints[36].



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Figure 1 Various organ involvement of the human body in cryptococcal infection. UTI: Urinary tract infection; CNS: Central nervous system.

Other major organs affected include the lungs, skin, soft tissues, and osteoarticular. Generalized lymphadenopathy with constitutional symptoms and weight loss can be a presentation that can mimic post transplant lymphoproliferative disease.

The typical signs of pulmonary involvement in a cryptococcus infection include fever, lethargy, night sweats, weight loss, sputum-producing cough, dyspnea, hemoptysis, and rarely severe respiratory failure. Only about one-third of people with cryptococcosis have a lung-only disease, which is usually part of an infection that has spread to other parts of the body[30]. A chest X-ray may reveal multiple or a single nodule, nodular or alveolar infiltrates, a cavitary lesion, a consolidation, a mass, or a pleural effusion. One-third or more of patients with pulmonary cryptococcosis may be asymptomatic[37]. Compared to patients with consolidations, pleural effusions, and infiltrates, patients with nodular densities or mass lesions were less likely to be symptomatic. Rarely severe cryptococcal infection especially with lung involvement can be complicated by the development of hemophagocytic lymphohistiocytosis (HLH) associated with very high mortality. A high index of suspicion is needed to make an early diagnosis which can help to incorporate specific therapy for HLH earlier which may improve outcomes[38].

Rarely, skin involvement is also seen with cryptococcal infection. Studies have shown that skin involvement can be the first sign of a disseminated cryptococcal illness[39]. Primary cutaneous cryptococcosis may act as a portal of entry for secondary disseminated cryptococcosis. Skin lesions might include cellulitis, panniculitis, subcutaneous nodules, abscesses, and acneiform papules. Umbilicated papules resembling *Molluscum contagiosum* are often present in hemogenous cryptococcal skin changes.

Another condition for the disease's localized form is cryptococcoma[33]. Most of them are recognized radiologically. Localized cryptococcal lesions typically coexist with a systemic illness. These are more typical in infections caused by *Cryptococcus gattii*. Cryptococcoma mainly affects the CNS and very infrequently the lungs and the transplanted kidney.

Both symptomatic cryptococcal pyelonephritis and graft involvement have been reported in cryptococcal infection[40]. Laryngeal cryptococcus and renal arterial rupture related to cryptococcus have also been described[41,42].

DIAGNOSIS OF CRYPTOCOCCAL INFECTION

Diagnosis can be challenging, especially in transplant recipients. One must have a high index of suspicion and a low diagnostic threshold to diagnose cryptococcosis, especially in regions with high prevalence. Any clinical signs of disease like subacute headache, fever, cough and weakness should prompt rapid cryptococcal testing. All transplant recipients with suspected or proven cryptococcosis should undergo a thorough evaluation for extrapulmonary sites of infection including a lumbar puncture [large volume cerebrospinal fluid (CSF) sample] and blood/urine cultures. This is important

to delineate the site and extent of disease in order to decide the duration of antifungal treatment. The methods used to confirm the infection include direct microscopic examination, culture, histopathology, serology and molecular detection. Antigen tests from blood or culture are rarely positive unless there is disseminated cryptococcal infection.

Imaging: CNS and chest

Cerebral cryptococcosis are more common with *C. gatti* than with *C. neoformans* infection. Normal brain imaging always does not exclude meningoencephalitis. Magnetic resonance imaging (MRI) (magnetic resonance imaging) brain is the preferred modality of imaging to diagnose cerebral cryptococcosis. The MRI findings of CNS cryptococcosis are leptomeningeal/pachymeningeal enhancement, dilated perivascular space, cryptococcal granuloma, hydrocephalus, miliary nodule and plexitis which can occur in isolation or in various combinations[43]. Chest imaging in pulmonary infection is non-specific with solitary/ multiple nodules or diffuse interstitial infiltrates[37].

CSF examination: The CSF picture in cryptococcal meningoencephalitis classically demonstrates increased opening CSF pressure, low white cell count with a mononuclear predominance, and slightly elevated protein with low/normal glucose concentration[44]. Neuroimaging should be done prior to lumbar puncture to exclude hydrocephalus and mass lesions. Cryptococcal antigen testing from the CSF or serum is the preferred strategy to diagnose infection. India ink testing on CSF is no longer recommended because it can miss low burden infections due to the low sensitivity and specificity.

Microscopy and culture

Visualization of encapsulated yeast forms with narrow budding in the sputum, bronchoalveolar lavage (BAL) or lung tissue biopsy specimens is suggestive of cryptococcal infection. The pellet from pleural fluid or BAL can be mixed with India Ink and observed under a microscope[45]. A lung biopsy from a nodule of uncertain aetiology requires a fungal culture to be done, in addition to a histopathology examination. Samples for culture should be placed on Sabouraud dextrose agar at 30°C for 7 d, in aerobic conditions, and observed daily[46]. *Cryptococcus* appears as mucoid creamy colonies. *C. neoformans* are identified generally as smooth colonies while *C. gattii* mostly appears as mucoid colonies. Canavanine-glycine-bromothymol blue (CGB) agar can be used to differentiate between *C. neoformans* and *C. gattii*. Colonies of *C. neoformans* will not cause changes in CGB agar. On the other hand, *C. gattii* produces a blue colour in CGB agar.

Histopathology

A lung biopsy is the best diagnostic option when sputum or bronchoscopy specimens are unavailable or negative. Gamori's methenamine silver or periodic acid Schiff stain identifies the organism as narrow-based budding yeasts (4-10 µm), usually surrounded by thick capsules in the lung tissue. Mucicarmine stain can be used to highlight the cryptococcal capsule as rose burgundy. Histopathological methods and cryptococcal antigen testing cannot differentiate between *C. neoformans* and *C. gattii*[47]. Lung histopathology in pulmonary cryptococcal infection varies from well-formed granulomas to minimal inflammation. Positive histology does not always correlate with culture result. A negative culture might be caused by nonviable organisms in the sample[30]. Figure 2 shows the histopathology of a patient with pulmonary cryptococcosis (H & E stain) and Figure 3 shows the histopathology of a patient with pulmonary cryptococcosis (Alcian blue -PAS stain). India Ink of *Cryptococcus neoformans* is provided in Figure 4.

Cryptococcal antigen testing

Capsular polysaccharides of *Cryptococcus* can be detected by using specific anti *C. neoformans* antisera in the serum, CSF, BAL, and urine by two formats- the latex agglutination test and the recently approved lateral flow immunoassay (LFA)[48]. LFA is the preferred method recommended for diagnosis given its low cost and high sensitivity. These cryptococcal antigen (CrAg) detection tests are rapid, sensitive and specific for diagnosis. These tests have not been standardised for respiratory specimens such as BAL, pleural fluid, or sputum. Pulmonary cryptococcal infection is usually associated with false negative serum CrAg, probably because of the low fungal burden outside the lung or the capsule-deficient strain of *Cryptococcus*[37]. Serum CrAg titres are typically higher in patients with disseminated diseases/CNS involvement. A prozone effect can occur in high cryptococcal burden states and recognition of this with appropriate dilution of the sample may be required.

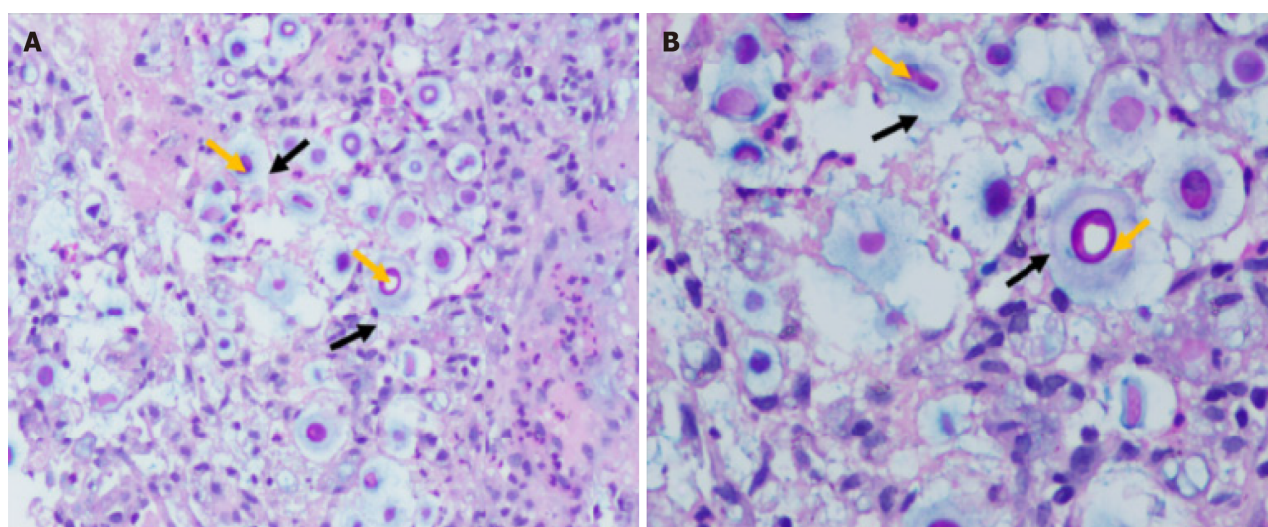
Molecular detection

This may be required in specific situations where other diagnostic tests have failed to confirm the diagnosis. These molecular methods include pan-fungal polymerase chain reaction (PCR), deoxyribonucleic acid sequencing for identification, multiplex PCR, isothermal amplification method, and probe-based microarrays. Species identification of *Cryptococcus* is also important as it may affect the choice of antifungal therapy and affect the clinical outcomes. Where possible, isolates should be subjected to either PCR or matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) for genotypic identification. Antifungal susceptibility testing is routinely not recommended for cryptococcal infection[49]. However, in patients with *C. neoformans* infection who have failed primary therapy or relapsed, or in patients with recent antifungal exposure (*i.e.* antifungal prophylaxis), antifungal susceptibility testing for fluconazole is recommended[50]. Table 1 shows modalities for the diagnosis of post-transplant cryptococcosis.

Table 1 Modalities for the diagnosis of post-transplant cryptococcosis

Method	Advantages	Disadvantages
Direct microscopic examination	Cryptococcus is identified as narrow budding encapsulated yeasts after mixing sample with India ink.	Direct microscopic examination
Culture	Identify the species and susceptibility patterns	Time consuming. More than 1 wk must elapse for fungal growth to occur
Histopathology	Gomori methenamine silver, and periodic acid-Schiff are used to detect Cryptococcus that appears as narrow-based budding yeasts (4-10 µm), usually surrounded by thick capsules in the lung tissue	Histopathology
Antigen detection	Inexpensive point-of-care testing, simple, cheap and rapid diagnosis in developing country, high sensitivity and specificity	Isolated pulmonary cryptococcal infection is usually associated with false negative serum CrAg, probably because of the low fungal burden outside the lung or the capsule-deficient strain of Cryptococcus. One must be aware of the prozone effect while interpreting these tests
Molecular detection	Required in specific situations where other diagnostic tools have failed to confirm a diagnosis of cryptococcosis, highly specific (almost 100%)	Expensive and not routinely available

CrAg: Cryptococcal antigen.



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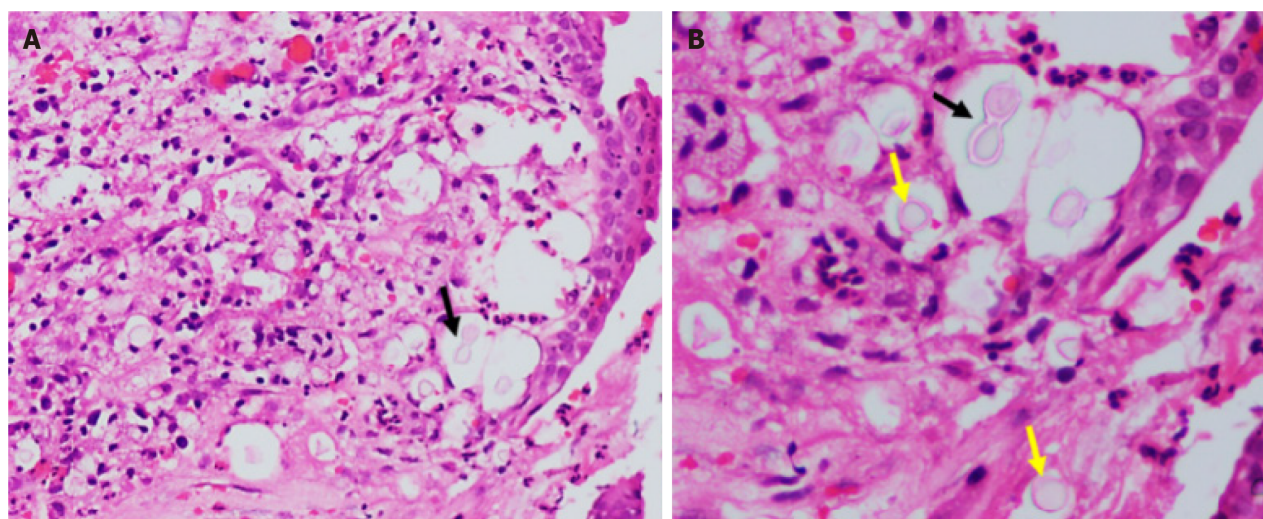
Figure 2 Histopathology of a patient with pulmonary cryptococcosis, hematoxylin and eosin stain and Alcian blue stain. A: At ×100 magnification; B: At ×200 magnification. Alcian blue-PAS stain attains the yeast forms of cryptococcus. Alcian blue stains the capsule blue colour (black arrow) and PAS stains the cell wall of the yeast magenta colour (yellow arrow).

TREATMENT

Much of the data on the treatment of patients with cryptococcal infections has been extrapolated from trials on HIV Infected patients[51] and also retrospective data from kidney and other SOT patients as there are no randomized controlled trials for the therapy[52-54]. Recommendations herein are consistent with the guidelines of the American Society of Transplantation Infectious Diseases[50].

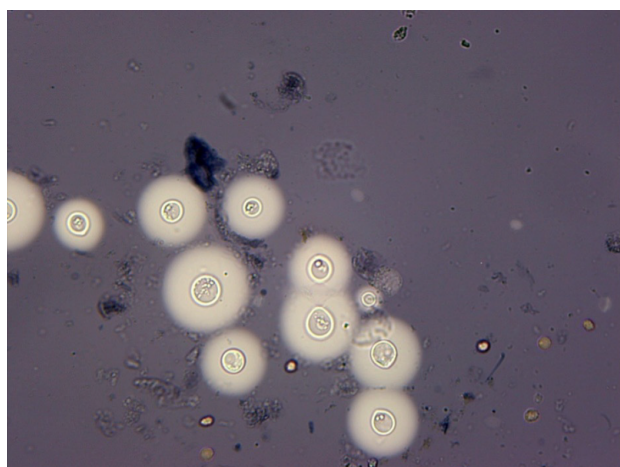
Management of cryptococcus has 3 main aspects

Antifungal therapy: As discussed, earlier patients with Cryptococcal infections can present with either isolated pulmonary involvement, neurological involvement or disseminated disease. The Therapy thus also depends on the site and extent of involvement: (1) In patients with CNS disease, Disseminated Disease or Moderate to severe pulmonary involvement the antifungal therapy of choice in kidney transplant recipients would be Liposomal Amphotericin B. Conventional amphotericin B is nephrotoxic and found to be inferior to the liposomal form on comparison of 90-d mortality between the two forms[54,55]. The addition of 5-flucytosine as a part of induction therapy reduces the chances of treatment failure[56]. The induction therapy is usually followed by a consolidation phase and maintenance phase. Doses of flucytosine and Fluconazole should be adjusted according to the glomerular filtration rate. Monitoring of flucytosine level is recommended (2 h post-dose 30-80 mcg/mL). Extended doses may be required as per clinical status. Figure 5 shows therapy for patients with CNS disease, Disseminated Disease or Moderate to severe Pulmonary



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Figure 3 India ink of cryptococcus neoformans. Endobronchial mucosa shows squamous metaplasia and the sub epithelium shows inflammatory exudates along with variably sized round to oval encapsulated yeast (yellow arrow) with thin walls and narrow based budding (black arrow). A: At $\times 100$ magnification; B: At $\times 200$ magnification.



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Figure 4 India ink-stained cryptococcus neoformans.

involvement; and (2) In patients with mild pulmonary disease use of fluconazole 400 mg/d for 6-12 mo is recommended. Even asymptotically detected (Cryptococcus positive on Sputum culture) pulmonary disease needs to be treated with the same regimen. In all these cases extrapulmonary disease should be excluded. Longer duration of Induction should be considered for patients who are clinically deteriorating, persistent comatose state, and persistently elevated intracranial pressure[16]. In case flucytosine is not available an extended duration of amphotericin B can be used lasting 4-6 wk. Use of extended-spectrum azoles like itraconazole, Voriconazole, Posaconazole, Isavuconazole, do not offer any advantage over fluconazole, but should be used in fluconazole-resistant *C. gatti*[57,58].

Supportive therapy: (1) Management of elevated Intracranial Pressure: 50% to 70% of patients with cryptococcal meningitis have elevated intracranial pressure due to reduced CSF absorption secondary to a film formed over the pial layer due to significant inflammatory response. This is a significant factor in morbidity and mortality of the patient as it can lead to hydrocephalous, blindness deafness or death[59]. Lumbar puncture should be done in all patients and opening pressure should be noted. If pressure is above 25 mmHg then a large volume of CSF should be removed, and attempts should be made to keep it below 20 mmHg using repeated lumbar puncture or by using drains from CSF cavities to the peritoneum[60]. Maintaining pressures below 25mmhg was associated with 69% relative survival protection[61]; and (2) Use of Dexamethasone: When Dexamethasone was added to adjunctive therapy on HIV patients showed slower clearance of CSF, Increased serious infections and no impact on mortality compared to placebo. But can be used after clearance of infection[62,63].

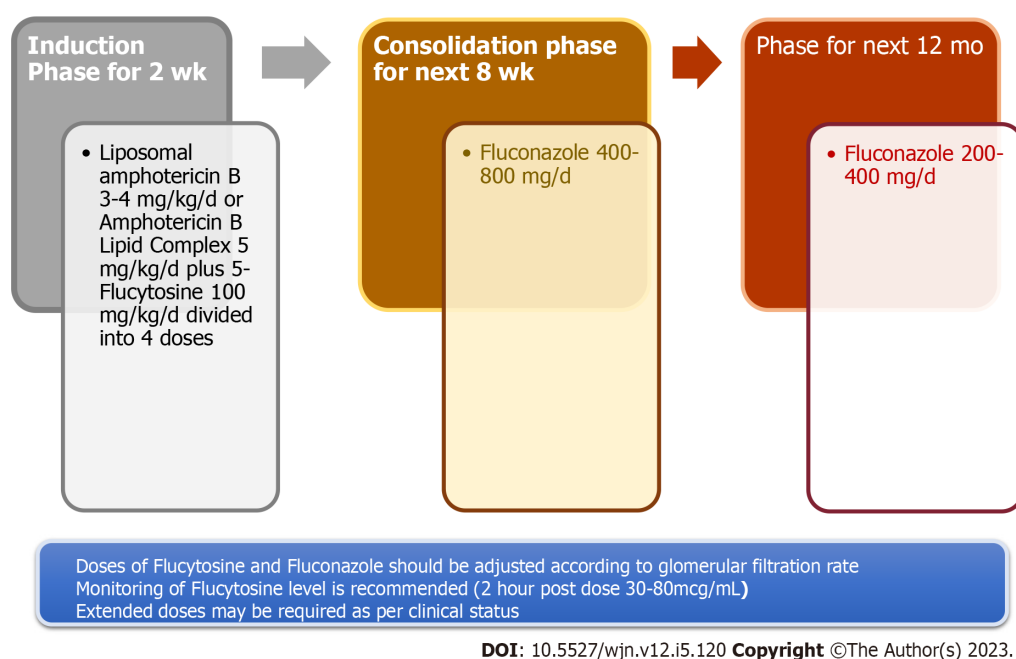


Figure 5 Therapy for patients with central nervous system disease, disseminated disease or moderate to severe pulmonary involvement.

Change in immunosuppression: As this disease is a direct result of the immunocompromised state of the patient there should be an attempt to reduce the immunosuppressive medications. Although nothing can be done about the T cell depleting agents given in the beginning slow reduction in dose of other immunosuppression with a low threshold for diagnosis of rejection should be done aiming for eradication of the fungus and preservation of allograft. The overall immunosuppression should be minimized during therapy; however, the specific approach to achieve this must be tailored to each individual instance. The expeditious decrease in the administration of immunosuppressive drugs may give rise to unfavorable consequences, including the occurrence of organ rejection and/or immune reconstitution inflammatory syndrome (IRIS). Therefore, it is advisable to strategically implement a progressive decrease in dosage with the administration of antifungal therapy. The primary objective is to achieve complete elimination of the infection while simultaneously ensuring the maintenance of allograft functionality. The interaction of azoles with CNI should be kept in mind and frequent monitoring of levels along with dose reduction should be done. The reduction of immunosuppression in KTR along with antifungal therapy initiation can also lead to the development of IRIS[64]. The incidence of this is 5%-12% in SOT recipients and it mimics a worsening cryptococcal disease and can also lead to rejection and graft loss[21,24,65]. It occurs 4-6 wk after initiation of the therapy and is found to be associated more with CNS disease and stoppage of CNI[16,66]. After ruling out the presence of fungi in the body IRIS can be tackled by increasing the dose of corticosteroids [64,67].

Prognosis and outcomes

Mortality rates in organ transplant recipients with cryptococcosis range from 33%-42% and may be as high as 49% in those with CNS disease and as low as 2.8% in those with isolated pulmonary involvement[2,21,50,51]. Recently, Ponzio *et al*[65] demonstrated an overall mortality rate of 49%. Independent risk factors for mortality include abnormal mental status, renal failure at baseline, fungemia and disseminated infection[24]. Patients receiving tacrolimus are less likely to have central nervous system involvement and more likely to have skin, soft-tissue, and osteoarticular involvement. Improved outcomes with the use of calcineurin-inhibitor agents may be attributable in part to their synergistic interactions with antifungal agents[5,68]. A significant percentage of patients (up to 20%) progress to graft loss after the infection[55]. Risk factors for graft loss after cryptococcosis include disseminated infection, higher baseline creatinine levels, graft dysfunction concomitant with amphotericin B deoxycholate therapy and an additional nephrotoxic condition [56]. Therefore, the clinical focus should be on the use of less nephrotoxic lipid formulations of amphotericin B in this specific population.

CONCLUSION

Cryptococcal infection accounts for < 10% of IFI and is seen in the late transplant period. Mortality rates are higher for those with meningeal involvement. The advent of newer diagnostic modalities and treatment has reduced infection-related morbidity but has not yet been able to reduce mortality beyond a level. Newer therapeutics with liposomal Amphotericin B, Fluconazole, and 5-flucytosine have improved survival. However, a significant proportion of these

patients progress to graft loss either due to reduced immunosuppression, infection or nephrotoxic therapeutic agents. Early detection however has resulted in better survival in the subset of patients.

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FOOTNOTES

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Retrospective Cohort Study

Effectiveness and safety of apixaban and rivaroxaban vs warfarin in patients with atrial fibrillation and chronic kidney disease

Sylvie Perreault, Laurie-Anne Boivin Proulx, Aurélie Lenglet, Ziad A Massy, Marc Dorais

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Abstract

BACKGROUND

Randomized controlled trials (RCTs) of direct oral anticoagulants (DOACs) included a low proportion of atrial fibrillation (AF) patients with chronic kidney disease (CKD), and suggested that DOACs are safe and effective in patients with mild-to-moderate CKD. In a metanalysis of RCTs and observational studies, DOACs were associated with better efficacy (*vs* warfarin) in early CKD and had similar efficacy and safety profiles in patients with stages IV-V CKD. But few studies have provided data on the safety and effectiveness of each DOAC *vs* warfarin in patients with stage III CKD. The effectiveness and safety of DOACs in those patients are still subject to debate.

AIM

To assess and compare the effectiveness and safety of apixaban and rivaroxaban *vs* warfarin in this patient population.

METHODS

A cohort of patients with an inpatient or outpatient code for AF and stage III CKD who were newly prescribed apixaban and rivaroxaban was created using the administrative databases from the Quebec province of Canada between 2013 and 2017. The primary effectiveness outcome was a composite of ischemic stroke, systemic embolism, and death, whereas the primary safety outcome was a composite of major bleeding within a year of DOAC *vs* warfarin initiation. Treatment groups were compared in an under-treatment analysis using inverse probability of treatment weighting and Cox proportional hazards.

RESULTS

A total of 8899 included patients filled out a new oral anticoagulation therapy claim; 3335 for warfarin and 5564 for DOACs. Compared with warfarin, 15 mg and 20 mg rivaroxaban presented a similar effectiveness and safety composite risk. Apixaban 5.0 mg was associated with a lower effectiveness composite risk [Hazard ratio (HR) 0.76; 95% confidence interval (CI): 0.65-0.88] and a similar safety risk (HR 0.94; 95%CI: 0.66-1.35). Apixaban 2.5 mg was associated with a similar effectiveness composite (HR 1.00; 95%CI: 0.79-1.26) and a lower safety risk (HR 0.65; 95%CI: 0.43-0.99). Although, apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95%CI: 0.65-0.88), but a similar safety risk profile (HR 0.94; 95%CI: 0.66-1.35). The observed improvement in the effectiveness composite for apixaban 5.0 mg was driven by a reduction in mortality (HR 0.61; 95%CI: 0.43-0.88).

CONCLUSION

In comparison with warfarin, rivaroxaban and apixaban appear to be effective and safe in AF patients with stage III CKD.

Key Words: Atrial fibrillation; Chronic kidney disease; Direct oral anticoagulant; Effectiveness; Safety; Warfarin

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Core Tip: Compared to warfarin, rivaroxaban and apixaban appear to be effective and safe in atrial fibrillation patients with stage III chronic kidney disease (CKD) in real world. Rivaroxaban 15 mg and 20 mg presented a similar effectiveness and safety composite risk. However, apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, to a reduction in deaths. Appropriately sized randomized controlled trials are needed to confirm these findings in stage III CKD patients.

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INTRODUCTION

Patients with chronic kidney disease (CKD) often develop atrial fibrillation (AF) at a rate of more than twice that of the general population[1-3]. Because patients with both AF and CKD have a greater risk of systemic embolism and bleeding events, an effective therapy is challenging[4-6]. For patients with non-valvular AF (NVAf) requiring oral anticoagulation therapy (OAC), medical evidence suggests treatment with a direct oral anticoagulant (DOAC) over warfarin, including patients with stage I-IV CKD[7]. Despite these recommendations, warfarin remains the OAC of choice for most AF patients [8] as well as AF patients with moderate to severe CKD[9].

Although the randomized controlled trials (RCTs) of DOACs included a low proportion of AF patients with CKD, the results suggested that DOACs are safe and effective in patients with mild-to-moderate CKD (stages I-III CKD, using Cockcroft-Cault formula)[10-13]. In a metaanalysis of observational studies and RCTs, DOACs were found to be more effective (*vs* warfarin) in early CKD and had similar efficacy and safety profiles in patients with CKD stages IV-V as well as patients on dialysis[14]. Recent population-based studies of AF patients with CKD have also examined the effectiveness and safety of DOACs *vs* warfarin[15-22]. However, few of these studies examined the safety and effectiveness of individual DOACs *vs* warfarin, nor did they examine the impact of varying doses in patients with stage III CKD with respect to stroke, systemic embolic events, major bleeding, or death[16,23]. Therefore, we attempted to evaluate and compare the efficacy and safety of various DOACs, including low-dose rivaroxaban (15 mg once per day), standard-dose rivaroxaban (20 mg once per day), low-dose apixaban (2.5 mg twice per day), and standard-dose apixaban (5.0 mg twice per day) *vs* warfarin in AF patients with stage III CKD.

MATERIALS AND METHODS

We analyzed several Quebec health care claims databases, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[24]. The need for informed consent was waived by the local institutional research committee (University of Montreal, Montreal, Quebec, Canada). The study protocol complied with the ethical guidelines of the 1975 declaration of Helsinki and was approved by the institutional research committee of the University of Montreal.

Data sources

We assembled a cohort of inpatients or outpatients using the Med-Echo administrative databases (hospital discharge reports), medical services of the Régie de l'Assurance Maladie du Québec (RAMQ), and RAMQ public drug plans, all databases administered by the RAMQ[25-28]. The databases were linked *via* encrypted health insurance numbers. Information from these databases provided a complete picture of hospital admissions, medical services, and medication used, if the patient was still living in the Quebec province.

Population

We identified adult patients with AF from January 1, 2013, to December 31, 2017. AF was detected by searching for the international classification of diseases, 9th revision (ICD-9) codes 427.3, 427.31, or 427.32, or the international classification of diseases, 10th revision (ICD-10) code I48[29,30]. The first instance of AF coding was used to determine eligibility. The cohort was subsequently restricted to patients who filled a new prescription for rivaroxaban (15 mg or 20 mg once daily), apixaban (2.5 or 5.0 mg twice daily) or warfarin within a year of AF diagnosis. Few patients had a new prescription of either dabigatran or edoxaban, so they were not included in our analysis. The date of the first OAC claim was defined as the date of cohort entry. New OAC users were defined as those not exposed to any OACs in the year prior to the claim index date. Patients were also required to have had pharmacy coverage for at least 12 mo and enrollment in a drug health insurance plan for at least one year before cohort entry.

We also excluded patients with a code for any condition or procedure that might have impacted the choice of OAC and duration of treatment at discharge: Cardiac valve replacement or valve procedures in the five years before cohort entry; end-stage CKD (meaning being on dialysis), kidney transplant, dialysis, or coagulation deficiency in the three years before cohort entry; medical procedures (including cardiac catheterization, stent, coronary artery bypass grafting, cerebrovascular, or defibrillator) in the three months before cohort entry; deep vein thrombosis or orthopedic surgery in the six months before cohort entry.

Lastly, the cohort was restricted to patients with stage III CKD by using the algorithm 2 to identify CKD G3-5ND, and then applying the exclusion of CKD G4-5ND by using the algorithm 3 (as defined by a composite variable covering the ICD code, drug use, and consultations with a nephrologist, as identified in the administrative databases). The composite variable has been validated, with reference to medical chart reviews of older adults with CKD [the algorithm used for estimated glomerular filtration rate (eGFR) definition], and has presented good positive predictive values[31].

Exposure

Treatment with an OAC was checked against the prescription fulfillment dates and the number of days of medication supplied for each fill. Exposure to treatment was considered in all analyses. We consider a gap of less than 30 d between the end of a treatment period and a new fill corresponded to continuous treatment. Patients were censored when they discontinued a treatment, switched to another OAC, or to another dose level. Allowing a gap in treatment of up to 30 d is reasonable because of the DOACs' short half-life. Taking this definition into account, the adherence rate over the 12-mo assessment period was at least 92% for all included patients. The patient's OAC exposure and censored status were updated every 30 d.

Outcomes

The primary effectiveness outcome was a composite of ischemic stroke or systemic embolism (SE) and all-cause mortality. The primary safety outcome was a composite of major bleeding, defined as either intracranial hemorrhage, gastrointestinal bleeding, or major bleeding from other sites. The individual components of the safety and effectiveness outcomes were evaluated in a secondary analysis.

We identified the outcomes by screening the ICD-9 or ICD-10 codes for the primary diagnosis on inpatient claims (Supplementary Table 1). In earlier validation studies, these codes performed relatively well and gave positive predictive values of over 80%[32,33].

Patient demographics and clinical characteristics

We documented demographic variables upon cohort entry and determined the associated morbidities from the inpatient and outpatient ICD-9 and ICD-10 diagnostic codes recorded in the three years preceding the cohort entry[30-32]. Next, we used the patients' characteristics and associated comorbidities to calculate the CHADS₂ score (Supplementary Tables 2 and 3)[34] and the modified HAS-BLED score (Supplementary Tables 2 and 4). The comorbidity burden was scored with the Charlson-Deyo Comorbidity Index[35,36]. A frailty score was also calculated from the modified elders risk assessment in the two years preceding cohort entry[37,38]. Lastly, we assessed all drug prescriptions filled in the two weeks preceding the cohort entry.

Statistical analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of patients, according to the type of OAC used. The follow-up periods and the level of adherence were reported as the mean with standard deviation (SD) or the median with interquartile range. The adherence to treatment in the year of follow-up was calculated by dividing the total number of days of treatment by 365. When the dispensing periods overlapped, the full length of each filled claim was accounted for, and the start date of the second claim was shifted to the end of the previous claim.

For the main analyses of the primary effectiveness and safety composites in an on-treatment, we used an inverse probability of treatment weighting (IPTW) approach to account for differences in patient characteristics between treatment groups[39,40]. Four IPTW cohorts were created: (1) Rivaroxaban 15 mg *vs* warfarin; (2) rivaroxaban 20 mg *vs* warfarin; (3) apixaban 2.5 mg *vs* warfarin; and (4) apixaban 5.0 mg *vs* warfarin. We then used a multivariable logistic regression model to estimate the observed probability (according to propensity score matching) of being in the treatment group (rivaroxaban 15 mg, rivaroxaban 20 mg, apixaban 2.5 mg, and apixaban 5.0 mg), based on all the baseline covariates, and the impact of temporal trends accounted for in the analysis by including the date of cohort entry in the IPTW matching. By approximating the randomization used in RCTs, the IPTW approach establishes a pseudo-population, balances the treatment groups according to the covariates included in the model, and thus minimizes the impact of confounding biases in observational studies. All weights were stabilized by multiplying the IPTW weight by the marginal probability of being in the treatment group. Descriptive statistics were also used to summarize the baseline characteristics of each IPTW cohort. For baseline characteristics, only absolute standardized differences of 10% or more between the unadjusted cohort and the IPTW-adjusted cohort were considered meaningful[39]. We reported the outcomes per 100 person-years for each treatment in each IPTW population. Hazard ratios (HRs) with 95% CIs associated were estimated using Cox proportional hazards models for each of the four IPTW cohorts described above.

Patients were censored at the time of enrollment if they were in a non-governmental drug coverage plan, admitted to a long-term care facility, admitted to the hospital (for more than two weeks), or in the case of a safety or effectiveness endpoint or death (whichever occurred first). The patient's OAC exposure and censored status were updated every 30 d.

For the sensitivity analyses of the primary effectiveness and safety composites, we first estimated Cox proportional HRs for outcomes in an intent-to-treat analyses in which we removed the censoring criteria of drug discontinuation or switching, so that all patients were followed up for 365 d unless they were censored for another reason. We used an IPTW approach to account for differences in patient characteristics between treatment groups. We reported the outcomes per 100 person-years for each treatment in each IPTW population. HRs and 95% CIs associated were estimated using Cox proportional hazards models for each of the four IPTW cohorts described above.

Secondly, we provided a negative control outcomes analyses using the risk of diabetes complications (primary code of hospitalization (ICD-9: 250.1-250.9, 357.2, 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, E14.9). Lastly, we calculated an E-value to assess the impact of unmeasured confounding[41]. The E-value indicates how strongly an unmeasured confounder would have to be associated with use of apixaban 2.5 mg, or apixaban 5.0 mg *vs* warfarin and the outcomes to reduce the observed effect to the null, depending on the measured covariates. All analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC). A biomedical statistician performed statistical review of the study.

RESULTS

A total of 8899 included AF patients with stage III CKD filled a new OAC prescription: 3335 for warfarin, 744 for the 15-mg dose of rivaroxaban, 1064 for 20-mg rivaroxaban, 1674 for 2.5-mg apixaban, and 2082 for 5.0-mg apixaban (Figure 1). The frequency of warfarin prescriptions decreased over time and was associated with a concomitant increase in DOAC prescription (Figure 2). As of 2017, apixaban 5.0 mg was the most commonly initiated drug.

Demographic and clinical characteristics

The patients' unadjusted characteristics are summarized in Supplementary Tables 5-8. Compared with warfarin users, rivaroxaban 15 mg users were slightly younger (mean $\pm$ SD age: 83.0 $\pm$ 8.5 *vs* 82.6 $\pm$ 7.8, respectively) and had a lower mean $\pm$ SD Charlson-Deyo Comorbidity index (6.1 $\pm$ 3.4 *vs* 5.3 $\pm$ 3.5, respectively), a lower mean $\pm$ SD CHADS₂ score (3.1 $\pm$ 1.2 *vs* 2.8 $\pm$ 1.2, respectively) and a lower mean $\pm$ SD HAS-BLED score of 3.6 $\pm$ 1.3 *vs* 3.2 $\pm$ 1.3, respectively. Compared with users of warfarin, rivaroxaban 20 mg users were younger (mean $\pm$ SD age: 83.0 $\pm$ 8.5 *vs* 74.2 $\pm$ 9.2, respectively) and had a lower mean $\pm$ SD Charlson-Deyo Comorbidity index (6.1 $\pm$ 3.4 *vs* 4.7 $\pm$ 3.5, respectively), a lower mean $\pm$ SD CHADS₂ score (3.1 $\pm$ 1.2 *vs* 2.3 $\pm$ 1.2, respectively), and a lower mean $\pm$ SD HAS-BLED score (3.6 $\pm$ 1.3 *vs* 2.7 $\pm$ 1.3, respectively). Compared with warfarin users, apixaban 2.5 mg users were older (mean $\pm$ SD age: 83.0 $\pm$ 8.5 *vs* 86.5 $\pm$ 6.3, respectively), had a lower mean $\pm$ SD Charlson-Deyo Comorbidity index (6.1 $\pm$ 3.4 *vs* 5.4 $\pm$ 3.3, respectively), a similar mean $\pm$ SD CHADS₂ score of 3.1 $\pm$ 1.2 *vs* 3.0 $\pm$ 1.1, respectively), and a similar mean $\pm$ SD HAS-BLED score of 3.6 $\pm$ 1.3 *vs* 3.3 $\pm$ 1.3, respectively. And, compared with users of warfarin, apixaban 5.0 mg users were also younger (mean $\pm$ SD age: 83.0 $\pm$ 8.5 *vs* 78.0 $\pm$ 8.4, respectively), and had a lower mean $\pm$ SD Charlson-Deyo Comorbidity index (6.1 $\pm$ 3.4 *vs* 5.1 $\pm$ 3.5, respectively), a lower mean $\pm$ SD CHADS₂ score (3.1 $\pm$ 1.2 *vs* 2.6 $\pm$ 1.2, respectively), and a lower mean $\pm$ SD HAS-BLED score (3.6 $\pm$ 1.3 *vs* 3.0 $\pm$ 1.3, respectively). As shown in Table 1, demographic and clinical characteristics of cohorts of new OAC users with stage III CKD after IPTW from 2013 to 2017 are well balanced.

Total of patients in RAMQ database

Extraction criteria: All patients aged 18 and older who received a diagnosis of atrial fibrillation (AF) (medical claim or hospitalization) between 2005 and 2017	353841
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Inclusion criteria

Diagnosis of AF (medical claim or hospitalization) between 2013 and 2017	119169	(Excluded) (234672)
At least one dispensation of oral anticoagulant (warfarin or DOAC) within the year following the AF diagnosis. The date of the first anticoagulant dispensation was defined as the claim index date	65329	(53840)
Complete coverage by the RAMQ drug plan for the year preceding the claim index date	65254	(75)
No warfarin and no DOAC in the year preceding the claim index date	49945	(15309)

Exclusion criteria

No valvular replacement/procedures in the 5 years preceding the claim index date	47685	(Excluded) (2260)
No end-stage renal disease or dialysis (for a minimal period of 3 continuous mo) in the 3 years preceding the claim index date	47498	(187)
No kidney transplant in the 3 years preceding the claim index date	47494	(4)
No coagulation deficiency in the 3 years preceding the claim index date	47480	(14)
No hip/knee/pelvis fracture in the 6 wk preceding the claim index date	46509	(971)
No catheterization, coronary cerebrovascular or defibrillator procedures during the 3 mo preceding the claim index date	41652	(4857)
No absence of chronic kidney disease stage III	9308	(32344)

Among the 9308 patients

Number of users of:	
Warfarin:	3335
Dabigatran 110 mg:	263
Dabigatran 150 mg:	146
Rivaroxaban 15 mg:	744
Rivaroxaban 20 mg:	1064
Apixaban 2.5 mg:	1674
Apixaban 5 mg:	2082

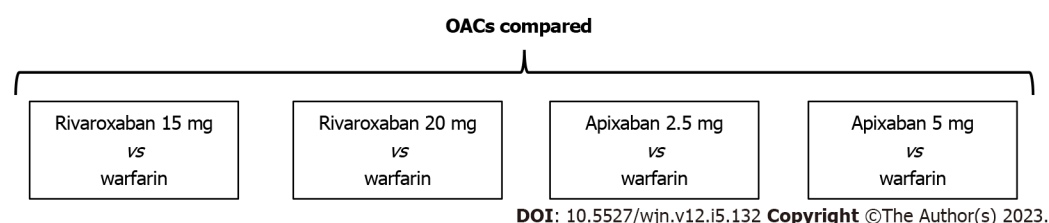


Figure 1 Study flow chart. No patients in the cohort received edoxaban, and patients using dabigatran were excluded for the low sample size between 2011-2017. DOAC: Direct oral anticoagulant; RAMQ: Régie d'Assurance Maladie du Québec.

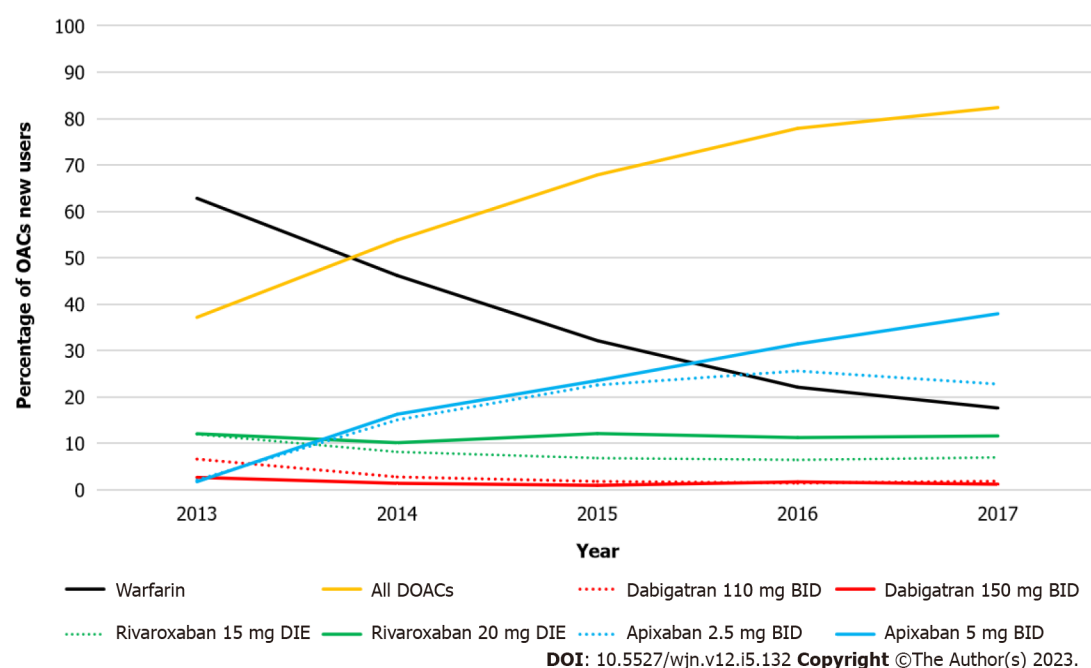


Figure 2 Changes in oral anticoagulant prescriptions from 2010 to 2017. DOACs: Direct oral anticoagulants; OAC: Oral anticoagulant.

Cumulative incidence in the IPTW cohorts

As shown in Table 1 and Supplementary Tables 5-8, there were no significant differences in baseline characteristics between the IPTW treatment groups. In Figures 3 and 4, we show the cumulative incidence curves for the effectiveness and safety composite outcomes in the IPTW in an on-treatment analysis. The follow-up times and levels of adherence are shown in Supplementary Tables 9 and 10.

HRs for effectiveness and safety outcomes in the IPTW cohorts

The annual rates and HRs for the primary analyses of the safety and effectiveness composites in the IPTW treatment groups in an on-treatment are shown in Supplementary Table 11. With warfarin as the reference group, we found rivaroxaban 15 mg and 20 mg had a similar effectiveness composite (HR 0.84; 95%CI: 0.60-1.18 and HR 0.83; 95%CI: 0.61-1.13, respectively) (Figure 5); and similar safety profile (HR 1.13; 95%CI: 0.70-1.83 and HR 1.29; 95%CI: 0.84-1.95, respectively). Apixaban 2.5 mg was similarly effective (HR 1.00; 95%CI: 0.79-1.26), but had a better safety profile (HR 0.65; 95%CI: 0.43-0.99), while apixaban 5.0 mg was associated with a better effectiveness (HR 0.76; 95%CI: 0.65-0.88), but a similar safety profile (HR 0.94; 95%CI: 0.66-1.35). A reduction in mortality (HR 0.61; 95%CI: 0.43-0.88) accounted for the observed improvement in the effectiveness composite for apixaban 5.0 mg.

Sensitivity analyses

The annual rates and HRs for the analyses of the effectiveness and safety composites in the IPTW treatment groups in an intent-to-treat are shown in Supplementary Table 12. Under intent-to-treat analyses, rivaroxaban 20 mg presented a better effectiveness composite (HR 0.79; 95%CI: 0.65-0.96), and the observed improvement in the effectiveness composite was due to a reduction in mortality (HR 0.72; 95%CI: 0.58-0.91) (Figure 6). Those point estimates are in relation to those observed in the IPTW treatment groups in an on-treatment, and the level of significance is linked to an increase of the number of events, particularly among those in the warfarin group.

As shown in Table 2, warfarin and DOACs had a similar rate of hospitalization per 100 person-years for diabetes complications, with no significant HRs. As we expected, all groups had similar results. In Table 3, we found the E-value closest to boundary 1 for the effectiveness composite and apixaban 5.0 mg *vs* warfarin was 1.53; hence, we suspect an

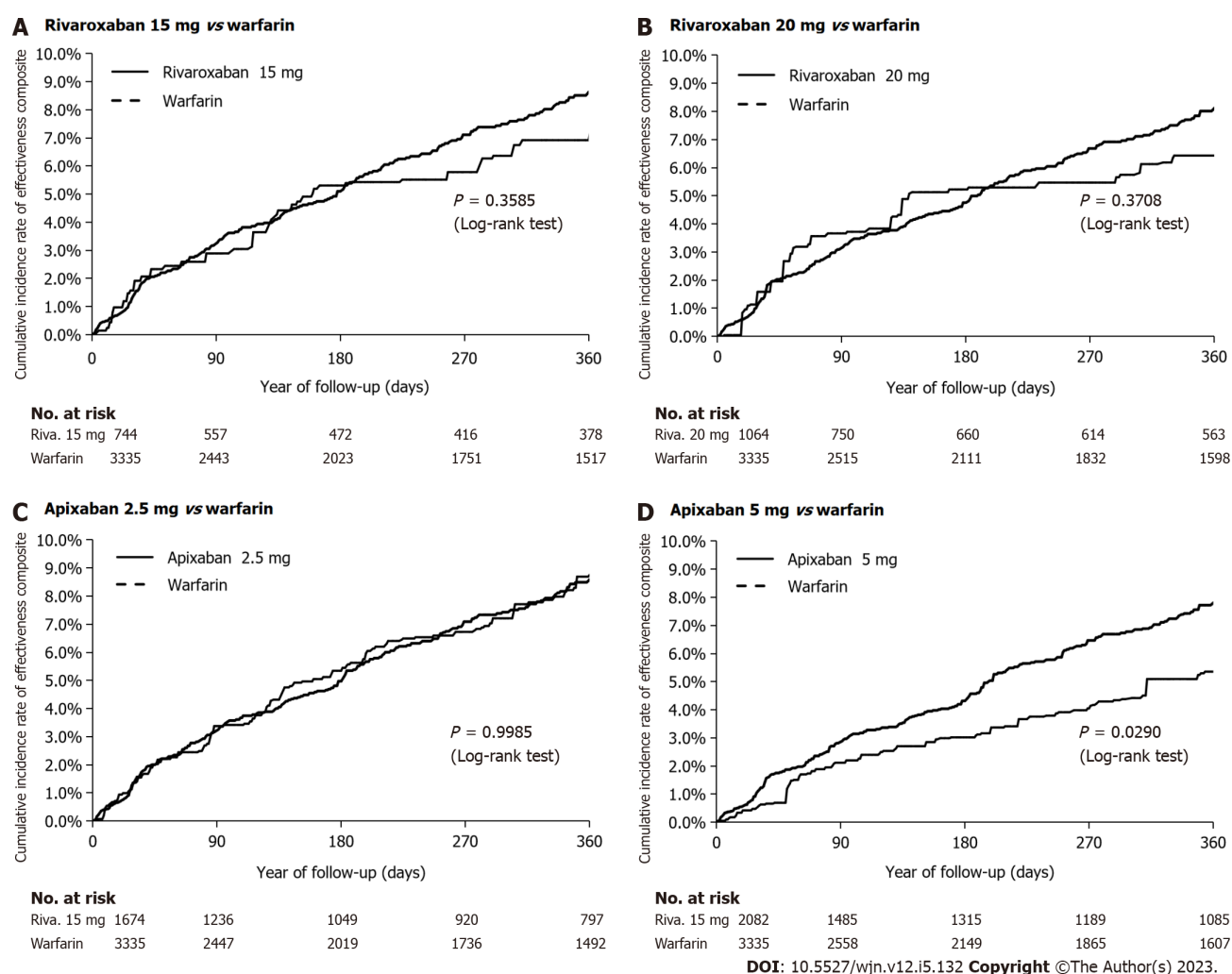


Figure 3 Cumulative rate of the primary effectiveness outcome after inverse probability of treatment weighting in an on-treatment analysis. A: Rivaroxaban 15 mg vs warfarin; B: Rivaroxaban 20 mg vs warfarin; C: Apixaban 2.5 mg vs warfarin; D: Apixaban 5 mg vs warfarin.

unmeasured confounder occurring 1.53 times more frequently in patients receiving apixaban 5.0 mg than in patients receiving warfarin, thus increasing the rate of safety composite events by a factor of 1.53. The high E-values indicate that the statistically significant results are robust with regards to unmeasured confounding factors.

DISCUSSION

The results of our cohort analysis provided several insights relevant to clinical practice. Firstly, DOAC prescription increased substantially over time, whereas warfarin prescription fell concomitantly. Nevertheless, over 10% of AF patients with stage III CKD were still being prescribed warfarin in 2017. Secondly, relative to warfarin, rivaroxaban appears to be safe and effective in AF patients with stage III CKD. Apixaban 2.5 mg might even have better safety profiles than warfarin; and for apixaban 5.0 mg, this difference in effectiveness was mainly driven by a reduction in deaths.

The increase in DOAC prescription is in line with the latest AF guidelines from the Canadian society of cardiology and European society of cardiology, which recommend DOAC therapy over warfarin for patients with NVAf and stage III CKD[7,42]. This recommendation is based on a sub-analysis of AF RCTs, which demonstrated that along with the DOACs' logistic advantages *vs* dose-adjusted warfarin, these drugs are no worse or even better than warfarin for reducing the risk of AF-associated stroke or SE in AF patients with stage III CKD, with a lower or similar major bleeding risk[10-13]. A meta-analysis of RCTs and observational trials of AF patients with CKD showed that DOACs can provide a significant reduction in stroke/SE (HR 0.81; 95%CI: 0.68-0.97) and a nonsignificant reduction in major bleeding (HR 0.87; 95%CI: 0.69-1.05) in stage III CKD, when compared with warfarin[14].

Very little data exists regarding the effectiveness and safety of individual DOACs and the impact of various doses on patients with stage III CKD. Most of the existing data comes from observational studies[15-21]. Data from a sub-analysis of the Aristotle trial demonstrated that apixaban can effectively reduce the occurrence of stroke, major bleeding, and mortality compared to that of warfarin among patients with impaired renal function (≤ 50 mL/min), when using creatinine-based estimates of GFR[13]. Wetmore *et al*[23] examined Medicare data from 22739 AF patients with stage III-

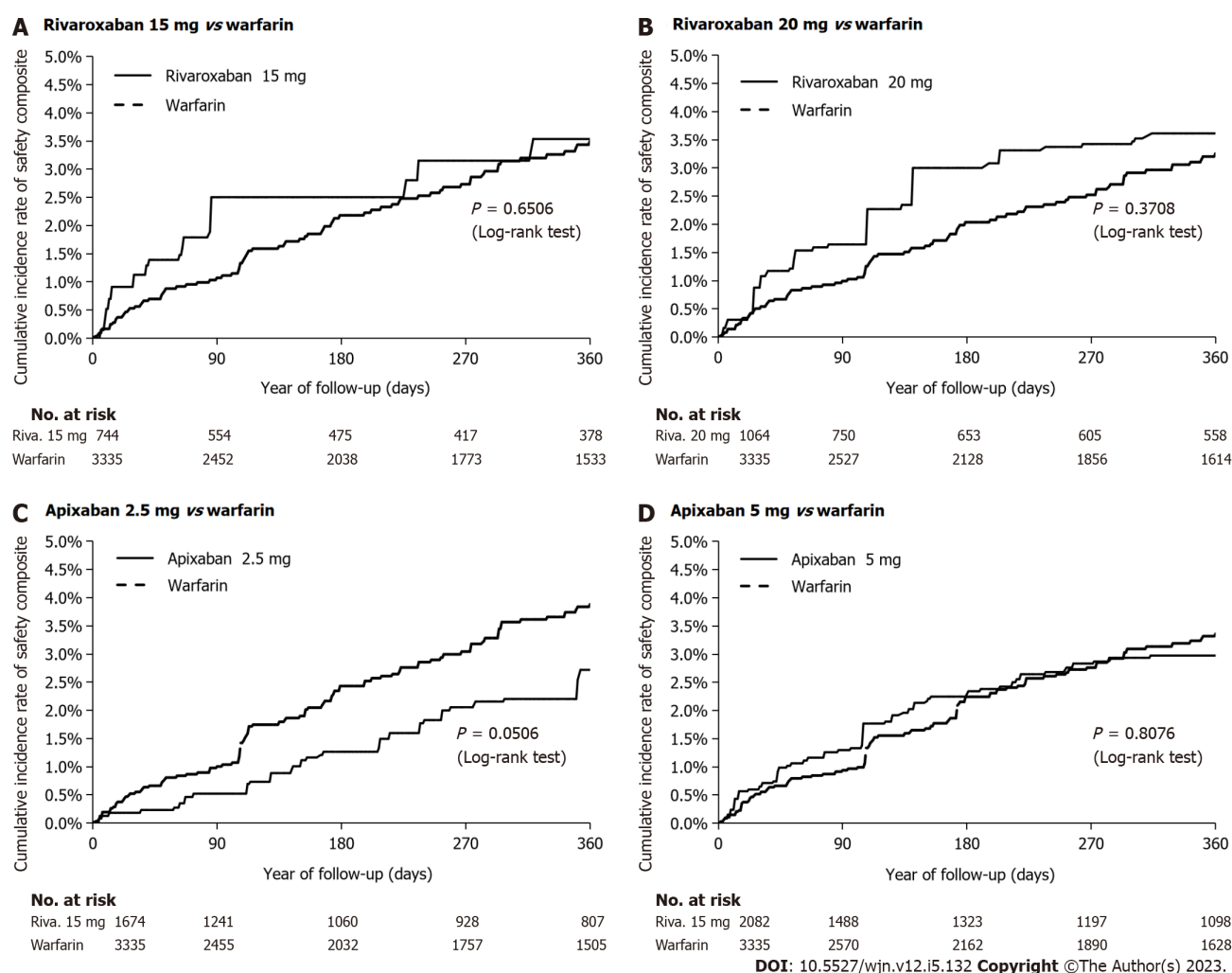


Figure 4 Cumulative rate of the primary safety outcome after inverse probability of treatment weighting in an on-treatment analysis. A: Rivaroxaban 15 mg vs warfarin; B: Rivaroxaban 20 mg vs warfarin; C: Apixaban 2.5 mg vs warfarin; D: Apixaban 5 mg vs warfarin.

IV CKD and found that apixaban reduced stroke/SE (HR 0.70; 95%CI: 0.51-0.96) and risk of major bleeding (HR 0.47; 95%CI: 0.37-0.59). Using electronic health record data, Fu *et al*[43] examined the safety and effectiveness of rivaroxaban *vs* warfarin in 555 stage III CKD AF patients and found a similar risk of stroke (HR 0.60; 95%CI: 0.23-1.56) and major bleeding (HR 0.73; 95%CI: 0.38-1.41). A subanalysis of the ROCKET-AF trial found that rivaroxaban 20 mg daily had a better efficacy profile in patients with a creatinine clearance (CrCl) of 50 mL/min or more but that rivaroxaban 15 mg daily had a similar efficacy profile in patients with a CrCl of 30-49 mL/min; the safety profile was similar for both CrCl categories[44]. Nonetheless, dose adjustment yielded results consistent with the overall trial, when compared with dose-adjusted warfarin[11]. Wetmore *et al*[23] found that in AF patients with stage III-IV CKD, rivaroxaban was associated with similar risks of stroke/SE (HR 0.80; 95%CI: 0.54-1.17) and major bleeding (HR 1.05; 95%CI: 0.85-1.30). However, the investigators did not report data on the effectiveness and safety of each dose level of DOAC *vs* warfarin in stage III CKD AF patients specifically.

Likewise, very few published studies have examined the impact of DOAC therapy *vs* warfarin on mortality, and also per specific dose. Makani *et al*[17] examined electronic health record data on 21733 AF patients with CKD and found that DOACs reduce the risk of all-cause mortality for all CKD classes. When examining individual DOACs in an on-treatment analysis, Wetmore *et al*[23] found a reduction in mortality for apixaban (HR 0.90; 95%CI: 0.84-0.96) but not for rivaroxaban (HR 0.95; 95%CI: 0.88-1.02) or dabigatran (HR 0.92; 95%CI: 0.84-1.01). These results might be explained by the fact that DOACs are associated with a lower incidence of renal adverse outcomes in patients with mild-to-moderate CKD, including declined renal function, a doubling in the serum creatinine level, or acute kidney injury[45]. Moreover, warfarin treatment is associated with an elevated risk of vascular and cardiac valve calcification[46-48], which in turn is associated with greater cardiovascular morbidity and mortality rates[49].

The present study has several strengths. First, it is one of the few large, real-world comparative studies of the effectiveness, safety, and mortality rates associated with individual DOACs and their dose levels *vs* warfarin. Second, we analyzed the single-payer health care claims database across the province of Quebec. Given that: (1) Most such clinical events result in an administrative claim, and (2) few patients in the province travel outside of Quebec for medical treatment, the study may likely have captured the vast majority of clinically significant events; which might not have been the case in previous single-hospital or single-insurer studies. Third, we performed IPTW cohorts by accounting for

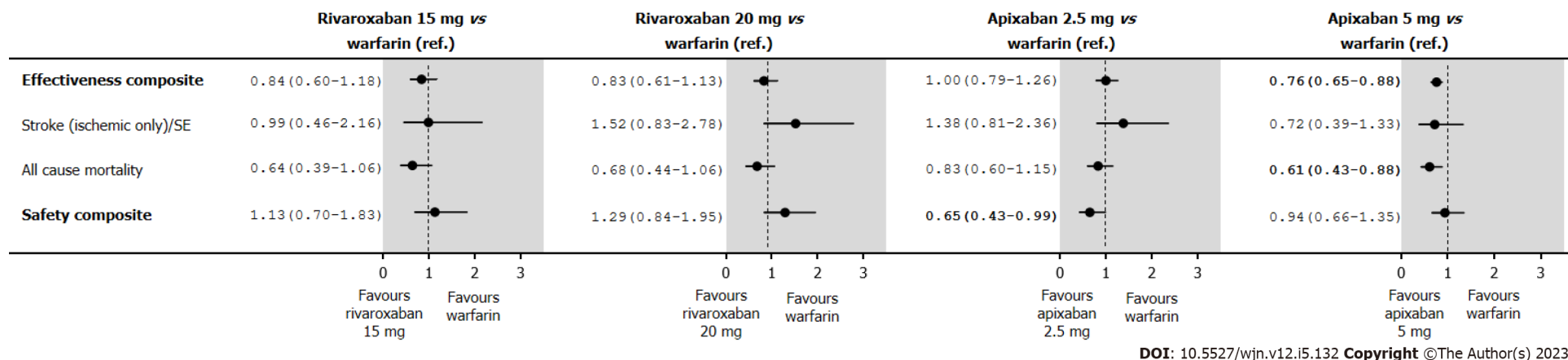


Figure 5 Hazard ratios (95% confidence interval) of effectiveness and safety outcomes in an on-treatment after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease. SE: Systemic embolism.

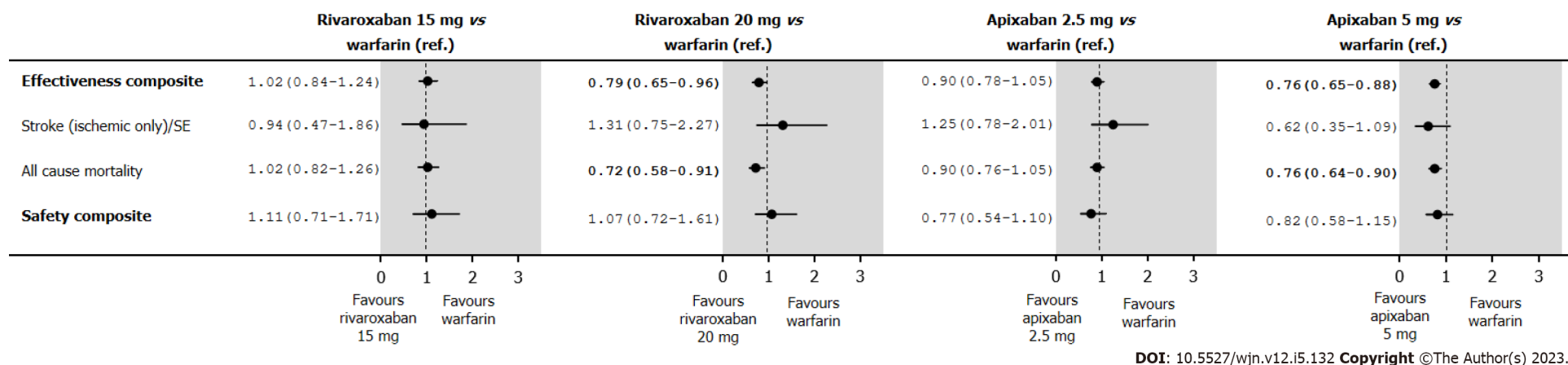


Figure 6 Hazard ratios (95% confidence interval) of effectiveness and safety outcomes in an intent-to-treat after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease. SE: Systemic embolism.

Table 1 Demographic and clinical characteristics of cohorts of new oral anticoagulation therapy users with stage III chronic kidney disease after inverse probability of treatment weighting from 2013 to 2017 (mean $\pm$ SD, %)

	IPTW warfarin and rivaroxaban 15 mg		IPTW warfarin and rivaroxaban 20 mg		IPTW warfarin and apixaban 2.5 mg		IPTW warfarin and apixaban 5.0 mg	
	Warfarin (<i>n</i> = 3335)	Rivaroxaban 15 mg (<i>n</i> = 744)	Warfarin (<i>n</i> = 3335)	Rivaroxaban 20 mg (<i>n</i> = 1064)	Warfarin (<i>n</i> = 3335)	Apixaban 2.5 mg (<i>n</i> = 1674)	Warfarin (<i>n</i> = 3335)	Apixaban 5.0 mg (<i>n</i> = 2082)
Age (yr)	82.9 $\pm$ 8.6	82.8 $\pm$ 7.7	80.1 $\pm$ 10.8	79.1 $\pm$ 8.2	84.3 $\pm$ 8.3	84.5 $\pm$ 7.2	80.4 $\pm$ 10.2	80.2 $\pm$ 7.8
Female sex	56.5	56.5	54.8	52.3	58.2	59.0	54.3	53.9
CHA ₂ DS ₂ -VASc	4.1 $\pm$ 1.4	4.1 $\pm$ 1.3	3.9 $\pm$ 1.5	3.9 $\pm$ 1.5	4.2 $\pm$ 1.4	4.2 $\pm$ 1.3	3.9 $\pm$ 1.5	3.8 $\pm$ 1.3
CHADS ₂ score	3.0 $\pm$ 1.2	3.0 $\pm$ 1.2	2.8 $\pm$ 1.3	2.9 $\pm$ 1.2	3.0 $\pm$ 1.2	3.0 $\pm$ 1.1	2.9 $\pm$ 1.3	2.8 $\pm$ 1.1
HAS-BLED score	3.5 $\pm$ 1.3	3.5 $\pm$ 1.3	3.3 $\pm$ 1.5	3.4 $\pm$ 1.4	3.5 $\pm$ 1.3	3.5 $\pm$ 1.2	3.3 $\pm$ 1.4	3.3 $\pm$ 1.2
Charlson-Deyo Comorbidity Index	5.9 $\pm$ 3.4	6.0 $\pm$ 3.6	5.7 $\pm$ 3.5	5.9 $\pm$ 3.6	5.9 $\pm$ 3.4	5.8 $\pm$ 3.2	5.7 $\pm$ 3.5	5.7 $\pm$ 3.4
Frailty score	18.6 $\pm$ 6.2	18.6 $\pm$ 5.9	17.7 $\pm$ 6.7	17.6 $\pm$ 6.3	18.8 $\pm$ 6.2	18.8 $\pm$ 5.8	17.7 $\pm$ 6.6	17.5 $\pm$ 6.1
Comorbidities (including the index hospitalization and the three years prior to cohort entry)								
Hypertension	86.2	86.5	83.9	85.2	86.9	86.9	84.5	84.0
Coronary artery disease	64.7	65.1	62.0	62.7	64.1	62.5	61.2	58.4
Acute myocardial infarction	21.1	20.3	18.9	17.5	20.9	20.9	18.8	15.8
Chronic heart failure	56.2	56.7	53.4	54.2	56.1	56.6	53.3	53.6
Cardiomyopathy	7.9	8.3	7.7	8.7	7.4	7.1	8.2	7.8
Other cardiac dysrhythmias	18.8	19.0	17.8	16.4	19.2	19.4	18.2	18.0
Valvular heart disease	26.1	27.1	24.9	24.6	25.7	25.6	23.5	22.3
Stroke/TIA	16.9	17.2	16.0	17.3	16.8	16.1	15.9	15.0
Peripheral vascular disease	27.7	27.5	26.6	25.9	27.3	26.2	25.6	23.2
Dyslipidemia	54.4	53.3	54.2	55.8	53.9	54.0	55.5	53.8
Diabetes	45.1	46.1	46.4	49.9	43.1	42.7	47.3	46.9
Major bleeding	38.5	38.3	37.0	39.3	38.3	37.0	36.2	34.8
Major intracranial bleeding	3.7	3.7	3.5	5.7	3.9	3.5	4.2	3.8
Major gastrointestinal bleeding	8.3	9.5	7.9	7.7	8.7	8.1	7.9	7.9
Other sites of major bleeding	32.0	30.9	30.9	32.4	31.8	31.2	29.8	28.8
Liver disease	2.6	2.8	2.9	2.9	2.5	2.4	2.7	2.5
Chronic obstructive pulmonary disease/asthma	44.0	44.2	46.0	49.7	42.2	42.1	44.5	45.3
Depression	11.8	11.5	12.2	11.8	11.7	11.4	12.1	11.9
Medical procedures (three years prior to cohort entry)								
Cardiac catheterization	5.0	5.4	5.2	5.3	5.0	4.9	6.4	6.4
Percutaneous coronary intervention-stent	4.1	3.9	3.8	4.1	3.8	4.0	4.1	4.0
Coronary artery bypass grafting	0.6	0.5	0.8	0.7	0.5	0.5	1.2	1.2
Implantable cardiac device	0.1	0.1	< 0.1	< 0.1	< 0.1	0.0	< 0.1	0.0

Medications (two weeks prior to cohort entry)								
Statin	51.0	51.2	51.1	52.9	50.0	47.9	50.6	50.4
Antiplatelet	8.7	8.5	8.1	8.9	8.3	7.4	8.1	7.9
Low-dose ASA	35.3	35.5	34.8	35.2	35.6	34.9	33.9	33.4
Proton pump inhibitors	49.7	49.6	47.8	46.9	50.0	49.1	46.4	44.7
NSAIDs	0.9	0.9	1.3	1.6	0.9	1.0	1.2	1.2
Digoxin	9.3	10.6	9.1	10.1	9.2	9.0	8.9	8.7
Amiodarone	9.6	9.3	8.6	6.1	9.3	9.8	8.8	8.0
Antidepressants	10.5	10.1	10.4	10.5	10.6	10.3	10.2	10.4
Beta-blockers	62.5	63.1	61.4	61.1	63.8	62.8	62.4	62.5
Calcium channel blockers	42.9	42.6	41.9	39.8	42.7	43.2	41.4	41.0
Inhibitors of the renin-angiotensin system	37.5	36.9	38.1	38.5	38.0	36.5	38.0	38.3
Diuretics	60.5	60.3	61.4	61.0	61.0	60.8	60.3	60.4
Loop diuretics	56.2	55.8	57.0	54.4	56.4	56.7	55.4	56.3
Antidiabetics	27.4	28.0	28.7	30.3	26.5	25.8	29.2	29.3
Health medical services (one year prior to cohort entry)								
Consultations with specialist physicians	1.2 ± 2.4	1.2 ± 1.9	1.2 ± 2.5	1.2 ± 2.3	1.2 ± 2.4	1.2 ± 2.2	1.2 ± 2.6	1.2 ± 1.8
Consultations with family physicians	1.3 ± 3.3	1.3 ± 2.8	1.2 ± 3.1	1.2 ± 2.5	1.3 ± 3.4	1.4 ± 3.0	1.2 ± 3.2	1.2 ± 2.6
Emergency visits	3.4 ± 3.1	3.4 ± 2.9	3.4 ± 3.4	3.5 ± 3.0	3.4 ± 3.1	3.5 ± 2.9	3.4 ± 3.3	3.3 ± 2.8
Health hospital services (three years prior to cohort entry)								
All-cause hospital admission	2.5 ± 2.1	2.5 ± 2.0	2.5 ± 2.4	2.6 ± 2.2	2.4 ± 2.0	2.5 ± 1.9	2.5 ± 2.3	2.4 ± 2.0

ASA: Acetylsalicylic acid; CKD: Chronic kidney disease; IPTW: Inverse probability of treatment weighting; NSAIDs: Nonsteroidal anti-inflammatory drugs; OAC: Oral anticoagulant; TIA: Transient ischemic attack.

Table 2 Sensitivity analysis of negative controls after inverse probability of treatment weighting in an on-treatment analysis

	Incident rate of rivaroxaban 15 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI) [†]	P value
Diabetes complications	1.1 (0.2-2.0)	1.1 (0.6-1.5)	1.02 (0.40-2.60)	0.96
	Incident rate of rivaroxaban 20 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI) [†]	P value
Diabetes complications	1.5 (0.6-2.4)	1.0 (0.6-1.5)	1.48 (0.72-3.06)	0.29
	Incident rate of apixaban 2.5 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI) [†]	P value
Diabetes complications	0.8 (0.3-1.3)	1.2 (0.8-1.7)	0.66 (0.31-1.41)	0.28
	Incident rate of apixaban 5.0 mg 100 PY (95%CI)	Incident rate of warfarin 100 PY (95%CI)	HR (95%CI)	P value
Diabetes complications	0.7 (0.2-1.1)	1.4 (0.9-1.9)	0.49 (0.24-1.02)	0.06

A significant value is for $P < 0.05$ *vs* warfarin.

[†]For the negative control, we assessed the risk of diabetic complications (ICD-9: 250.1-250.9, 357.2, and 366.41; ICD-10: E10-E14 excluding E10.9, E11.9, E12.9, E13.0, and E14.9).

CI: Confidence interval; HR: Hazard ratio; PY: Person-years.

Table 3 E-values for significant comparisons in an on-treatment analysis after inverse probability of treatment weighting of new oral anticoagulant users with stage III chronic kidney disease

	Hazard ratio (95%CI)	E value corresponding to the CI bound closest to 1	E value for hazard ratio point estimate ¹
Apixaban 2.5 mg <i>vs</i> warfarin			
Safety composite	0.65 (0.43-0.99)	1.11	2.45
Apixaban 5.0 mg <i>vs</i> warfarin			
Effectiveness composite	0.76 (0.65-0.88)	1.53	1.96
All-cause mortality	0.61 (0.43-0.88)	1.53	2.66

¹E-value for hazard used the point estimate instead of the bound closest to 1.

CI: Confidence interval.

confounding effects in our primary analysis and we provided several sensitivity analyses.

Our study also had some limitations. First, observational studies of administrative data are subject to confounding bias by unadjusted factors, such as the severity of AF, the exact eGFR, the international normalized ratio, body weight, over-the-counter prescriptions, and ethnicity. Second, use of administrative claims depends on comprehensive, accurate coding and recording of all diagnoses, drugs, and procedures. Third, it might not be possible to generalize our results to younger patients, or patients treated with other DOACs (dabigatran and edoxaban). Fourth, the effect sizes for individual safety and effectiveness outcomes were small. Fifth, we could not use time spent in the therapeutic range to assess the appropriateness of warfarin dosing, since our database did not record the international normalized ratio. Finally, our study did not include exact eGFR values; however, we estimated eGFR using an algorithm known to be valid in older adults[31].

CONCLUSION

In this observational study of new OAC users with AF and stage III CKD, we found that rivaroxaban is safe and effective relative to warfarin but if CrCl is between 30-49 mL/min, we need to reduce the dose to 15 mg. Apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, including a reduction in deaths. Appropriately sized RCTs are needed to confirm these findings in stage III CKD patients.

ARTICLE HIGHLIGHTS

Research background

The effectiveness and safety of apixaban and rivaroxaban in patients with atrial fibrillation (AF) and stage III chronic kidney disease (CKD) are not well established.

Research motivation

Few studies have evaluated the safety and efficacy of individual direct oral anticoagulants *vs* warfarin, nor have they established how dose selection impacts patients with AF and stage III CKD with respect to the incidence of stroke/systemic embolism (SE), major bleeding, and death.

Research objectives

We assessed and compared the effectiveness and safety of standard-dose rivaroxaban, low-dose rivaroxaban, standard-dose apixaban, and low-dose apixaban *vs* warfarin in a representative group of patients with AF and stage III CKD.

Research methods

A cohort of new users of apixaban, rivaroxaban or warfarin in AF patients and stage III CKD was created using administrative databases. We defined the effectiveness as a composite of stroke, SE or death; safety was defined as a composite of major bleeding within 1-year of follow-up. Comparisons were under treatment analysis using inverse probability of treatment weighting and Cox models.

Research results

Rivaroxaban 15 mg and 20 mg were associated with a similar efficacy and safety composite risk *vs* warfarin. Apixaban 5.0 mg was linked with decreased effectiveness composite risk [hazard ratio (HR) 0.76; 0.65-0.88] and a similar safety risk

(HR 0.94; 0.66-1.35), compared with apixaban 2.5 mg, which was associated with a similar effectiveness composite (HR 1.00; 0.79-1.26) and a lower safety risk (HR 0.65; 0.43-0.99).

Research conclusions

This observational study of new users of rivaroxaban and apixaban find that both appear to be safe and effective compared to warfarin in patients with AF and stage III CKD. Apixaban 2.5 mg might even have a better safety profile than warfarin, while apixaban 5.0 mg might have a better effectiveness profile than warfarin, to a reduction in deaths.

Research perspectives

The research perspective should be an appropriately sized randomized controlled trials to confirm these findings in AF patients with stage III CKD.

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FOOTNOTES

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Retrospective Cohort Study

Bleeding complications after percutaneous kidney biopsies – nationwide experience from Brunei Darussalam

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Abstract

BACKGROUND

Kidney biopsy serves as a valuable method for both diagnosing and monitoring kidney conditions. Various studies have identified several risk factors associated with bleeding complications following the procedure, but these findings have shown inconsistency and variation.

AIM

To investigate the risk of bleeding complications following percutaneous kidney biopsy in Brunei Darussalam. We sought to explore the relevant clinical and pathological risk factors associated with these complications while also considering the findings within the broader international literature context.

METHODS

We conducted a retrospective study of all adult patients who underwent kidney biopsy in Brunei Darussalam from October 2013 to September 2020. The outcomes of interest were post-biopsy bleeding and the need for blood transfusions. Demographics, clinical, laboratory and procedural-related data were collected. Logistic regression analysis was used to identify predictors of outcomes.

RESULTS

A total of 255 kidney biopsies were included, with 11% being performed on transplanted kidneys. The majority of biopsies were done under ultrasound guidance (83.1%), with the rest under computer tomography guidance (16.9%). The most common indications for biopsy were chronic kidney disease of undefined cause (36.1%), nephrotic syndrome (24.3%) and acute kidney injury (11%). Rate of bleeding complication was 6.3% – 2% frank hematuria and 4.3% perinephric hematoma. Blood transfusion was required in 2.8% of patients. No patient lost a kidney or died because of the biopsy. Multivariate logistic regression identified baseline hemoglobin [odds ratio (OR): 4.11; 95% confidence interval (95% CI): 1.12-15.1; $P = 0.03$ for hemoglobin ≤ 11 g/dL vs. > 11 g/dL] and the

presence of microscopic hematuria (OR: 5.24; 95%CI: 1.43-19.1; $P = 0.01$) as independent risk factors for post-biopsy bleeding. Furthermore, low baseline platelet count was identified as the dominant risk factor for requiring post-biopsy transfusions. Specifically, each $10 \times 10^9/L$ decrease in baseline platelet count was associated with an 12% increase risk of needing transfusion (OR: 0.88; 95%CI: 0.79-0.98; $P = 0.02$).

CONCLUSION

Kidney biopsies were generally well-tolerated. The identified risk factors for bleeding and transfusion can help clinicians to better identify patients who may be at increased risk for these outcomes and to provide appropriate monitoring and management.

Key Words: Kidney biopsy; Bleeding complications; Logistic regression; Retrospective cohort study; Risk

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Core Tip: This retrospective study in Brunei Darussalam examined kidney biopsies from 2013 to 2020 and identified key risk factors for post-biopsy bleeding complications. Notably, it revealed that the presence of microscopic hematuria is a significant, previously unrecognized risk factor for such complications. Other findings included the impact of low baseline hemoglobin levels and platelet counts on bleeding and transfusion risk. These insights can assist clinicians in identifying high-risk patients and improving post-biopsy monitoring and care. Overall, the study enhances our understanding of kidney biopsy outcomes and patient safety.

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INTRODUCTION

A kidney biopsy is a procedure used to diagnose and monitor kidney disease. However, it is not without risks, with bleeding being a major complication due to its invasive nature. Bleeding complications can range from self-limited hematuria and asymptomatic perinephric hematomas, to life-threatening hemorrhage that can lead to serious consequences such as hemodynamic instability, kidney loss, and even death. In current practice, kidney biopsies are commonly performed percutaneously using real-time ultrasound guidance, which has been shown to decrease the risk of complications[1,2]. Moreover, automated spring-loaded biopsy devices have been found to be more effective than hand-driven systems, resulting in a higher yield of glomeruli and a reduction in major complications[3-5].

The frequency of complications following percutaneous native kidney biopsies varies across studies, mainly due to differences in patient populations, procedural techniques, complication definitions, and post-procedural monitoring. Although several risk factors for bleeding complications have been identified in different studies, the findings have been inconsistent[6]. A recent systematic review and meta-analysis that included 118064 biopsies reported that hematomas occurred in 11% of cases, frank hematuria in 3.5%, bleeding requiring blood transfusions in 1.6%, and interventions to stop bleeding in 0.3%[7].

In this study, we aimed to further investigate the risk of bleeding complications after percutaneous kidney biopsy and explore the associated clinical and pathologic risk factors. The study focused on a cohort of patients who underwent biopsies in Brunei Darussalam. By analyzing this specific group, the researchers aimed to provide more insights into the local context and shed light on factors that may contribute to bleeding complications.

MATERIALS AND METHODS

Study design and population

In this retrospective study, medical records of adult patients aged 18 years and above were reviewed over a period of seven years, from October 1, 2013, to September 30, 2020. The objective was to identify major bleeding complications associated with kidney biopsies. The analysis included only the first biopsy for patients who had multiple procedures. Kidney biopsy requests made by renal physicians were included, while those requested by urologists for investigating kidney lesions were excluded. Prior to the biopsy, informed consent was obtained from each patient. All antiplatelet and anticoagulation medications were stopped at least five days before the procedure, following the guidelines of the Society of Interventional Radiology[8]. Coagulation tests were performed a day before the biopsy, and if required, they were corrected using fresh frozen plasma or vitamin K to normalize the results. Pre-biopsy desmopressin was not administered. The biopsies were carried out in an inpatient setting, under local anesthesia, and with the guidance of

imaging techniques such as ultrasound or computed tomography (CT). In all cases, Bard Max-Core™ disposable core biopsy instrument with 18-gauge needles were used, typically performing 2 or 3 passes in the lower left renal pole, with the patient in the prone position. The decision on the number of passes was made by the procedurist based on whether sufficient core samples were obtained. After the procedure, patients were prescribed strict bed rest in a supine position for at least 6 h and monitored for post-procedure hematuria. Imaging was conducted immediately after the biopsy to confirm hemostasis, but further imaging to detect perinephric hematoma was only performed if clinically necessary. Perinephric hematoma was defined as the presence of hematoma on imaging that was over 1 cm in any dimension. Full blood counts were routinely performed the next day, and blood transfusions were given if clinically indicated. The decision to resume antiplatelet medications for patients at high cardiovascular risk was made on an individual basis, considering the risks and benefits. The study adhered to the ethical standards outlined in the Declaration of Helsinki and received approval from the institutional review board. A waiver of consent was granted by the Medical and Health Research and Ethics Committee.

Outcomes and covariates

Data on biopsy-associated bleeding events were collected by review of patient records. Outcomes of interest were post-biopsy bleeding (frank hematuria and/or perinephric hematoma), the need for blood transfusions, angiographic or open surgical interventions to control bleeding, nephrectomy and death. The timings of these bleeding events in relation to the procedure were also recorded.

Covariates examined included demographics (age, gender, ethnicity, height, weight), clinical (presence of hypertension, diabetes, whether dialysis was required before biopsy, biopsy indication), pre-biopsy laboratory (hemoglobin, platelet, serum creatinine, urea, albumin, total cholesterol, urine red blood cell, urine protein:creatinine ratio) and procedural-related (native or graft kidney, right or left kidney, procedurist, ultrasound or CT guided, number of passes, number of cores obtained) data.

Statistical analysis

mean $\pm$ SD were calculated for continuous parametric data, and medians and interquartile ranges for non-parametric data. Categorical data were reported using frequencies. For group comparisons, we used the Student *t*-test, Mann-Whitney test, chi-square test or Fisher exact test, as appropriate.

Logistic regression analysis was used to identify risk factors associated with the outcomes. Univariate analysis was done for each variable, using the Wald test. Any variable with a significant univariate test at *P* value < 0.1 was then selected as a candidate for the multivariate model along with all variables of known biologic importance. We chose this *P* value cut-off point as more traditional levels such as 0.05 can fail in identifying variables known to be important.

Following the fit of the multivariable model, iterative process of variable selection was done where covariates were removed from the model if they were non-significant and not a confounder. Significant was evaluated at the 0.05 alpha level and confounding as a change in any remaining parameter estimate greater than 15% as compared to the full model. At the end of this iterative process, the model contains significant covariates and confounders. Any variable not selected for the original multivariate model is added back one at a time, with significant covariates and confounders retained earlier. Any that are significant at the 0.05 level are put in the model, and the model is iteratively reduced as before but only for the variables that were additionally added.

All statistical analyses were performed using STATA software application version 17.

RESULTS

Over the 7-year period, 255 kidney biopsies were performed (Tables 1 and 2). The mean age of the patients were 35.5 years old, with mean weight of 72.3 kg. Out of the total, 28 procedures (11%) were conducted on transplanted kidneys. Notably, those performed with CT-guidance (16.9%) tended to involve patients with a higher average weight compared to those guided by ultrasound scan (83.1%) – with mean weights of 92 kg *vs.* 68 kg, respectively (*P* < 0.001). Forty-six percent of the patients had history of hypertension and 21% had history of diabetes. The primary reasons for performing biopsies were as follows: Chronic kidney disease of unspecified cause (36%), nephrotic syndrome (24%), and acute kidney injury (AKI) (11%). 10.2% of patients needed dialysis pre-biopsy. This decision was left at the discretion of the attending nephrologists. The median pre-biopsy serum creatinine was 158 [interquartile range (IQR): 80 to 381] $\mu\text{mol/L}$, hemoglobin 11.5 ± 2.6 g/dL and platelet count $300 \pm 108.3 \times 10^9/\text{L}$. Out of the 255 kidney biopsies performed, only 5 patients exhibited minor abnormalities in their coagulation tests prior to the procedure. This 2% incidence was deemed statistically insignificant. Importantly, none of these 5 patients experienced any bleeding complications post-biopsy. Consequently, our team decided not to incorporate coagulation tests as predictive factors. Moreover, it is worth noting that the occurrence of post-biopsy bleeding could not be linked to abnormal coagulation test results, as all patients involved in this study displayed normal coagulation results or had their abnormalities corrected before the biopsy. The mean size of the biopsied kidney was 11 ± 1.4 cm. Majority (92.4%) needed two passes.

Bleeding complications were observed in 16 (6.3%) patients, with 4.3% developing a perinephric hematoma and 2% experiencing frank hematuria. These bleeding complications happened at a median of 1-hour (IQR: 1-15 h) post-biopsy. The maximum duration was a 48 h delay. Blood transfusion was needed in a total of 7 (2.8%) patients. As shown in Tables 3 and 4, both bleeding complications and need for blood transfusion were associated with very similar risk factors in the univariate analysis – the presence of microscopic hematuria, 4 needle passes (compared to 2 passes), lower baseline hemoglobin, platelet, complements, higher serum creatinine, urea, as well as anti-double stranded DNA and antinuclear

Table 1 Characteristics of study cohort (continuous variables)

Variables	N = 255	Missing
Mean age in years	35.5 ± 14.3	
Mean weight (kg)	72.3 ± 20.1	21
Mean hemoglobin (g/dL)	11.5 ± 2.6	1
Mean platelet ($\times 10^9/L$)	300 ± 108.3	1
Median creatinine ($\mu\text{mol/L}$)	158 (80-381)	
Median urea (mmol/L)	9.4 (5.5-15.8)	
Mean albumin (g/L)	30.1 ± 9.1	
Median cholesterol (mmol/L)	5.6 (4.6-8.2)	13
Median urine protein: Creatinine ratio (mg/mmol)	598 (239-1119)	20
Median 24hr urine total protein (g/day)	4.2 (1.7-7.8)	103
Mean complement C3 (g/L)	1 ± 0.4	43
Mean complement C4 (g/L)	0.28 ± 0.14	44
Mean size of biopsied kidney (cm)	11 ± 1.4	40

Table 2 Characteristics of study cohort (categorical variables)

Variables	Classifications	N = 255	Missing
Male gender		120 (47%)	
Ethnicity	Malay	207 (81.2%)	
	Chinese	6 (2.4%)	
	Indian	1 (0.4%)	
	Other	41 (16%)	
Presence of hypertension		116 (45.5%)	
Presence of diabetes		53 (20.8%)	
Dialysis before biopsy		26 (10.2%)	
Clinical syndrome	Isolated hematuria	4 (1.6%)	
	Isolated non-nephrotic proteinuria	25 (9.8%)	
	Hemo-proteinuria	26 (10.2%)	
	Nephritic syndrome	2 (0.8%)	
	RPGN	1 (0.4%)	
	Nephrotic syndrome	62 (24.3%)	
	Nephritic-nephrotic syndrome	10 (3.9%)	
	AKI	28 (11%)	
	CKD of undefined cause	92 (36.1%)	
	Other	5 (2%)	
Presence of urine RBC		108 (43.9%)	9
Presence of ANA		69 (29.5%)	31
Presence of anti-dsDNA		28 (15.5%)	74
Presence of ENA		28 (15.6%)	76
Presence of ANCA		8 (4.2%)	63
Presence of HBV		6 (2.6%)	27

Presence of HCV		2 (0.9%)	34
Presence of HIV		2 (1%)	45
Transplanted (<i>vs.</i> native) kidney		28 (11%)	
If native, right (<i>vs.</i> left) kidney		3 (1.3%)	
Procedurist	Radiologist 1	82 (34%)	15
	Radiologist 2	28 (11.6%)	
	Radiologist 3	68 (28.2%)	
	Radiologist 4	13 (5.4%)	
	Radiologist 5	49 (20.3%)	
	Radiologist 6	1 (0.4%)	
CT (<i>vs.</i> USS) guidance		43 (16.9%)	
Number of passes	1	1 (0.5%)	57
	2	183 (92.4%)	
	3	11 (5.6%)	
	4	3 (1.5%)	
Number of cores	1	3 (1.5%)	48
	2	188 (90.8%)	
	3	12 (5.8%)	
	4	4 (1.9%)	

RPGN: Rapidly progressive glomerulonephritis; AKI: Acute kidney injury; CKD: Chronic kidney disease; RBC: Red blood cell; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen antibodies; ANCA: Antineutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; CT: Computer tomography; USS: Ultrasound scan.

antibodies positivity.

Multivariable logistic regressions were performed to assess factors associated with an increased risk of bleeding complications and the need for blood transfusion after kidney biopsy. As indicated in Table 3, there is a significant association between pre-biopsy hemoglobin levels [with an odds ratio (OR) of 4.11; 95% confidence interval (95%CI): 1.12–15.1; $P = 0.03$ for hemoglobin 11 g/dL *vs.* >11 g/dL] and the presence of microscopic hematuria (with an OR of 5.24; 95%CI: 1.43–19.1; $P = 0.01$), both linked to the occurrence of post-biopsy bleeding.

After adjustment for other variables, it was solely the pre-biopsy platelet level that emerged as the primary factor influencing the need for post-biopsy blood transfusions. For every decrease of 10000/ μ L in the initial platelet count, there was a corresponding 12% rise in the likelihood of requiring a blood transfusion (with an OR of 0.88; 95%CI: 0.79–0.98; $P = 0.02$). There was no death, nephrectomy or angiographic or open surgical interventions needed to control bleeding. No differences in outcomes were found regarding the biopsy time period, first period from 2013 to 2016 years and second period from 2017 to 2020 (data not shown).

DISCUSSION

Our study has provided further evidence of the safety of kidney biopsy. We did not observe any nephrectomy or death after kidney biopsies performed in these 7 years. In a large meta-analysis, the rate of nephrectomy and death were 0.01% and 0.02% respectively[9].

The incidence of bleeding complications, specifically perinephric hematoma and frank hematuria, was found to be similar to that reported in other studies such as by Pombas *et al*[10] (5.44% hematoma, 2.57% frank hematuria) and Xu *et al*[11] (5.8% hematoma, 4.8% frank hematuria). However, two meta-analyses conducted by Poggio *et al*[7] and Corapi *et al* [9] have reported a higher incidence of hematoma at 11% and 11.6% respectively, while the incidence of frank hematuria was found to be comparable at 3.5% in both meta-analyses.

In our study, the 2.8% incidence of blood transfusion after kidney biopsy is consistent with the findings of other studies such as Shidham *et al*[12] (2.48%). However, our rate is lower compared to some population-based studies from other countries such as United States (26%)[13], Canada (9%)[14], France (5%)[15], Boston (4.3%)[16] and Australia (4%)[17]. Some of these population-based studies overestimated the risks of blood transfusion as not all of the events were attributable to kidney biopsies, particularly if the cohort had high co-morbidities such as anemia and heart failure. On the other hand, our rate of blood transfusion is higher than some other studies, such as Poggio *et al*[7] (1.6%), Pombas *et al*[10] (1.2%), Andrulli *et al*[18] (1.1%), Corapi *et al*[9] (0.9%), Tøndel *et al*[19] (0.9%) and Kawaguchi *et al*[20] (0.8%).

Table 3 Odds ratios for bleeding complications

Variables	Classifications	Univariate logistic regression			Multivariate logistic regression ¹		
		OR	95%CI	P value	OR	95%CI	P value
Age (yr)		1.02	0.99-1.06	0.254			
Gender	Female	Reference					
	Male	0.49	0.17-1.47	0.204			
Ethnicity	Malay	Reference					
	Chinese	2.55	0.28-23.2	0.407			
	Indian	NA	NA	NA			
	Other	NA	NA	NA			
Mean weight (kg)		1.01	0.98-1.04	0.428			
Hypertension	No	Reference					
	Yes	1.2	0.44-3.31	0.720			
Diabetes	No	Reference					
	Yes	1.8	0.60-5.42	0.297			
Dialysis before biopsy	No	Reference					
	Yes	2.16	0.57-8.13	0.256			
Clinical syndrome	AKI	Reference					
	Isolated hematuria	NA	NA	NA			
	Isolated non-nephrotic proteinuria	NA	NA	NA			
	Hemo-proteinuria	0.33	0.03-3.43	0.355			
	Nephritic syndrome	NA	NA	NA			
	RPGN	NA	NA	NA			
	Nephrotic syndrome	0.28	0.04-1.80	0.180			
	Nephritic-nephrotic syndrome	NA	NA	NA			
	CKD of undefined cause	1.02	0.26-3.98	0.982			
	Other	NA	NA	NA			
Mean hemoglobin (g/dL)	> 11	Reference			Reference		
	≤ 11	5.04	1.40-18.15	0.013 ²	4.11	1.12-15.1	0.033
Mean platelet ($\times 10^9/L$)	> 250	Reference					
	≤ 250	3.23	1.13-9.20	0.028 ²			
Median creatinine ($\mu\text{mol/L}$)	< 265	Reference					
	≥ 265	3.62	1.27-10.3	0.016 ²			
Median urea (mmol/L)	< 10	Reference					
	≥ 10	3.8	1.19-12.12	0.024 ²			
Mean albumin (g/L)		0.95	0.90-1.01	0.080 ²			
Median cholesterol (mmol/L)		0.91	0.75-1.11	0.346			
Presence of urine RBC	No	Reference			Reference		
	Yes	6.1	1.7-22	0.006 ²	5.24	1.43-19.1	0.012
Median urine protein:creatinine ratio (mg/mmol)		1	0.9996-1.0005	0.787			

Median 24 h urine total protein (g/day)		0.92	0.78-1.09	0.351
Mean complement C3 (g/L)	≥ 0.8	Reference		
	< 0.8	3.35	1.20-9.36	0.021 ²
Mean complement C4 (g/L)	≥ 0.15	Reference		
	< 0.15	3.41	1.10-10.5	0.033 ²
Presence of ANA	No	Reference		
	Yes	2.98	1.03-8.58	0.044 ²
Presence of anti-dsDNA	No	Reference		
	Yes	3.94	1.19-13.1	0.025 ²
Presence of ENA	No	Reference		
	Yes	1.89	0.48-7.48	0.363
Presence of ANCA		NA	NA	NA
Presence of HBV		NA	NA	NA
Presence of HCV		NA	NA	NA
Presence of HIV		NA	NA	NA
Kidney type	Native	Reference		
	Transplanted	0.52	0.07-4.10	0.536
Site of kidney		NA	NA	NA
Mean size of biopsied kidney (cm)	> 12	Reference		
	≤ 12	2.11	0.58-7.63	0.254
Procedurist	Radiologist 1	Reference		
	Radiologist 2	0.30	0.04-2.48	0.265
	Radiologist 3	0.51	0.15-1.73	0.277
	Radiologist 4	0.68	0.08-5.83	0.722
	Radiologist 5	0.17	0.02-1.38	0.101
	Radiologist 6	NA	NA	NA
Guidance	Ultrasound	Reference		
	CT	2.39	0.79-7.28	0.124
Number of passes	1	NA	NA	NA
	2	Reference		
	3	NA	NA	NA
	4	8.65	0.72-103.7	0.089 ²
Number of cores	1	35.6	2.97-426.6	0.005 ²
	2	Reference		
	3	NA	NA	NA
	4	5.93	0.57-62.3	0.138

¹Only *P* value < 0.05 in the multivariate analysis is shown.

²*P* value < 0.1.

OR: Odds ratio; 95%CI: 95% confidence interval; NA: Not applicable (as zero cell count); AKI: Acute kidney injury; RPGN: Rapidly progressive glomerulonephritis; CKD: Chronic kidney disease; RBC: Red blood cell; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen antibodies; ANCA: Antineutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; CT: Computer tomography.

Table 4 Odds ratios for blood transfusion

Variables	Classifications	Univariate logistic regression			Multivariate logistic regression ¹		
		OR	95%CI	P value	OR	95%CI	P value
Age (yr)		1.00	0.95-1.05	0.951			
Gender	Female	Reference					
	Male	0.44	0.08-2.33	0.338			
Ethnicity	Malay	Reference					
	Chinese	NA	NA	NA			
	Indian	NA	NA	NA			
	Other	NA	NA	NA			
Mean weight (kg)		0.99	0.95-1.04	0.809			
Hypertension	No	Reference					
	Yes	0.89	0.19-4.06	0.880			
Diabetes	No	Reference					
	Yes	0.63	0.07-5.31	0.667			
Dialysis before biopsy	No	Reference					
	Yes	NA	NA	NA			
Clinical syndrome	AKI	Reference					
	Isolated hematuria	NA	NA	NA			
	Isolated non-nephrotic proteinuria	NA	NA	NA			
	Hemo-proteinuria	NA	NA	NA			
	Nephritic syndrome	NA	NA	NA			
	RPGN	NA	NA	NA			
	Nephrotic syndrome	0.45	0.03-7.47	0.577			
	Nephritic-nephrotic syndrome	NA	NA	NA			
	CKD of undefined cause	1.55	0.17-13.9	0.694			
	Other	NA	NA	NA			
Mean hemoglobin (g/dL)	> 11	Reference					
	≤ 11	6.67	0.79-56.2	0.081 ²			
Mean platelet (10×10^9 /L)		0.88	0.79-0.98	0.021 ²	0.88	0.79-0.98	0.021
Median creatinine (μ mol/L)		1.001	0.999-1.003	0.105			
Median urea (mmol/L)		1.068	0.999-1.141	0.052 ²			
Mean albumin (g/L)		0.93	0.86-1.01	0.105			
Median cholesterol (mmol/L)		0.94	0.71-1.24	0.654			
Presence of urine RBC	No	Reference					
	Yes	8	0.95-67.5	0.056 ²			
Median urine protein:creatinine ratio (mg/mmol)		1	0.9997-1.0006	0.415			
Median 24 h urine total protein (g/day)		0.88	0.66-1.18	0.389			
Mean complement C3 (g/L)	≥ 0.8	Reference					

	< 0.8	6.32	1.20-33.3	0.030 ²
Mean complement C4 (g/L)	≥ 0.15	Reference		
	< 0.15	5.43	1.16-25.4	0.032 ²
Presence of ANA	No	Reference		
	Yes	6.39	1.21-33.8	0.029 ²
Presence of anti-dsDNA	No	Reference		
	Yes	12.6	2.18-72.5	0.005 ²
Presence of ENA	No	Reference		
	Yes	2.83	0.49-16.2	0.244
Presence of ANCA		NA	NA	NA
Presence of HBV		NA	NA	NA
Presence of HCV		NA	NA	NA
Presence of HIV		NA	NA	NA
Kidney type	Native	Reference		
	Transplanted	1.36	0.16-11.7	0.781
Site of kidney		NA	NA	NA
Mean size of biopsied kidney (cm)	> 12	Reference		
	≤ 12	1.18	0.22-6.19	0.849
Procedurist	Radiologist 1	Reference		
	Radiologist 2	NA	NA	NA
	Radiologist 3	0.79	0.13-4.86	0.797
	Radiologist 4	2.17	0.21-22.6	0.518
	Radiologist 5	0.54	0.05-5.36	0.600
	Radiologist 6	NA	NA	NA
Guidance	Ultrasound	Reference		
	CT	0.81	0.10-6.93	0.850
Number of passes	1	NA	NA	NA
	2	Reference		
	3	NA	NA	NA
	4	22.4	1.67-300.3	0.019 ²
Number of cores	1	23	1.71-308.7	0.018 ²
	2	Reference		
	3	NA	NA	NA
	4	15.3	1.30-181.4	0.030 ²

¹Only p-value < 0.05 in the multivariate analysis is shown.

²p-value < 0.1.

OR: Odds ratio; 95%CI: 95%confidence interval; NA: Not applicable (as zero cell count); AKI: Acute kidney injury; RPGN: Rapidly progressive glomerulonephritis; CKD: Chronic kidney disease; RBC: Red blood cell; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen antibodies; ANCA: Antineutrophil cytoplasmic antibodies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; CT: Computer tomography.

Our study found that patients with low baseline hemoglobin were more likely to experience bleeding complications, while those with low baseline platelet counts had an increased risk of requiring blood transfusion. This is consistent with findings from other studies, such as Pombas *et al*[10] and Xu *et al*[11]. Specifically, we observed that with every decrease of 10000/ μ L in the initial platelet count, there was a corresponding 12% rise in the likelihood of necessitating a blood transfusion. This is comparable to the 11% increase reported in the Xu *et al*[11] study.

To our knowledge, our study is the first to show that the presence of microscopic hematuria is associated with bleeding complication following kidney biopsy. The reasons for this association are unclear, and it is possible that unmeasured confounding factors may contribute to both hematuria from glomerular bleeding and bleeding post-biopsy. Therefore, further evaluation in larger, prospective studies is needed before changes are made to clinical practice. Interestingly, a recent study by Andrulli *et al*[18] found that high proteinuria levels may actually protect against bleeding complications after biopsy. It is therefore important that variables including urinalysis (hematuria and/or proteinuria) be included in the regression models in future studies, to better elucidate this association.

Numerous studies have reported increased bleeding complications and the need for blood transfusions to be associated with factors such as presence of hypertension[12,21], presence of diabetes[22], poor kidney function[9,18,23,24], female [17,25,26], elderly[9,27], larger biopsy needle[9,28], higher number of needle passes[18], AKI as indication for biopsy[7,9,11,26]. We have not found these variables to be significant risk factors in our cohort. It is important to note that different studies may use different definitions of bleeding complications, have variation in patient selection, procedural technique or monitoring protocols, leading to variability in findings. Analyses of predictors of complications associated with kidney biopsy also vary across studies.

Our study found that majority of bleeding complications were identified within the first 1-15 h of the biopsy, but a significant proportion (2%-10%) occurred after 24 h[12,14,29]. Specifically, we observed that 6% of patients with bleeding complications experienced them after 24 h. Therefore, it is crucial to consider the appropriate post-biopsy observation period based on individual patient risk.

A strength of our study is the nationwide investigation that allowed for an extensive and in-depth analysis of risk factors for post-biopsy bleeding complications in the current era. However, our study has some limitations that should be considered. Our findings are limited by the relatively small sample size which may limit the power to detect significant associations. Residual confounding is also likely to be present in the retrospective study design. Additionally, we did not collect data on certain potential predictors, such as blood pressure and coagulation tests. We also did not evaluate the impact of antiplatelet use as it is already standard practice to withhold. Furthermore, a recent meta-analysis found no significantly increased risk for major bleeding complications in patients on aspirin[30]. Another limitation is that repeat imaging post-biopsy was not routinely performed, unless prompted by patient symptoms or hemodynamic instability. This may have led to ascertainment bias and potential underestimation of hematoma events.

Notwithstanding these limitations, the identified risk factors can still be utilized in clinical practice to effectively risk stratify patients and inform shared-decision making. Counseling patients on these known risks is imperative to achieving patient-centered care. We strongly suggest that modifiable risk factors be managed aggressively to lower the risk of bleeding.

CONCLUSION

In conclusion, our study shows that the risk of bleeding after kidney biopsy performed by radiologists is generally low. However, we found that bleeding complications were more frequent in patients with lower pre-biopsy hemoglobin level and those with microscopic hematuria. Patients with lower platelet counts also had a higher likelihood of requiring blood transfusion after kidney biopsy. While our findings support the safety of kidney biopsy, it is important to carefully evaluate patients in order to minimize the risks associated with the procedure.

ARTICLE HIGHLIGHTS

Research background

Kidney biopsy serves as a valuable method for both diagnosing and monitoring kidney conditions. However, various studies have identified several risk factors associated with bleeding complications following the procedure, but these findings have shown inconsistency and variation.

Research motivation

Identifying key factors that significantly predict complications following a kidney biopsy is valuable in providing patients with essential information when seeking their consent for the procedure.

Research objectives

Our primary objective was to investigate the risk of bleeding complications following percutaneous kidney biopsy in Brunei Darussalam. We sought to explore the relevant clinical and pathological risk factors associated with these complications while also considering the findings within the broader international literature context.

Research methods

We performed a retrospective review of records of patients who underwent percutaneous kidney biopsies in Brunei Darussalam from October 1, 2013 to September 30, 2020. The demographic, clinical, laboratory and procedural-related characteristics of the patients were reviewed.

Research results

A total of 255 kidney biopsies were included. The incidence of bleeding (including hematuria and perinephric hematoma) stood at 6.3%. Blood transfusions were deemed necessary for 2.8% of patients, and fortunately, no patient suffered kidney loss or mortality due to the biopsy procedure. In a multivariable logistic regression analysis, two factors emerged as independent risk contributors for post-biopsy bleeding: baseline hemoglobin levels and the presence of microscopic hematuria. Additionally, a lower baseline platelet count emerged as the primary risk factor associated with the need for post-biopsy transfusions.

Research conclusions

Our findings align with existing research regarding the predictive risk factors for post-kidney biopsy bleeding complications. Nevertheless, our study uniquely highlights that the presence of pre-biopsy microscopic hematuria represents a notable and previously unreported risk factor for these complications.

Research perspectives

While our findings support the safety of kidney biopsy, it is important to carefully evaluate patients in order to minimize the risks associated with the procedure.

FOOTNOTES

Author contributions: Lim CY designed the research, contributed to the statistical analysis, literature review, writing and revision; Khay SL collected the data and contributed to the writing and revision; all authors approved the paper.

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Observational Study

The correlation of spot urinary protein-to-creatinine ratio with 24-h urinary protein excretion in various glomerulopathies

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Abstract

BACKGROUND

Proteinuria is an important and well-known biomarker of many forms of kidney injury. Its quantitation is of particular importance in the diagnosis and management of glomerular diseases. Its quantification can be done by several methods. Among these, the measurement of 24-h urinary protein excretion is the gold standard method. However, it is cumbersome, time-consuming, and inconvenient for patients and is not completely foolproof. Many alternative methods have been tested over time albeit with conflicting results. Among the latter, the measurement of urine protein-to-creatinine ratio (uPCR) in single-voided urinary samples is widely used. The majority of studies found a good correlation between uPCR in single urine samples with 24-h urinary protein estimation, whereas others did not.

AIM

To investigate the correlation of spot uPCR with 24-h urinary protein estimation in patients suffering from different forms of glomerulopathies at a single large-volume nephrological center in Pakistan.

METHODS

This cross-sectional, observational study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan from September 2017 to March 2018. All newly presenting adult patients with proteinuria who were being investigated for suspected glomerulonephritis and persistent proteinuria with ages between 18 to 60 years were enrolled. All patients were given detailed advice regarding 24-h urine collection starting at 7:00 AM for total protein and creatinine excretion estimations. A spot urine sample was collected the next day at the time of submission of a 24-h urine sample for

measuring uPCR along with a blood sample. The data of patients were collected in a proforma. SPSS version 20.0 was used for statistical analysis.

RESULTS

A total of 157 patients were included. Their mean age was 30.45 ± 12.11 years. There were 94 (59.8%) males and 63 (40.2%) females. The mean 24-h urinary protein excretion was 3192.78 ± 1959.79 mg and the mean spot uPCR was 3.16 ± 1.52 in all patients. A weak but significant correlation was observed between spot uPCR and 24-h urinary protein excretion ($r = 0.342$, $P = 0.01$) among all patients. On subgroup analysis, a slightly better correlation was found in patients older than 47 years ($r = 0.78$), and those with body mass index > 25 kg/m² ($r = 0.45$). The Bland and Altman's plot analysis comparing the differences between spot uPCR and 24-h protein measurement also showed a wide range of the limits of agreement between the two methods.

CONCLUSION

Overall, the results from this study showed a significant and weakly positive correlation between spot uPCR and 24-h urinary protein estimation in different forms of glomerulopathies. The agreement between the two methods was also poor. Hence, there is a need for careful interpretation of the ratio in an unselected group of patients with kidney disease.

Key Words: Glomerulopathies; 24-h proteinuria; Spot urinary protein-to-creatinine ratio; Correlation; Proteinuria; Agreement

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Core Tip: The quantitation of proteinuria is of particular importance in the diagnosis and management of glomerulonephritides. The measurement of 24-h urinary protein excretion is the gold standard. However, it is cumbersome, time-consuming, and inconvenient for patients. The measurement of urine protein-to-creatinine ratio (uPCR) is the most popular alternative. Numerous studies have been conducted on the correlation of these two methods with conflicting results. We assessed the correlation and the degree of agreement between the two methods. We conclude that uPCR shows poor correlation and poor agreement with 24-h proteinuria. It must be interpreted with caution in an unselected group of glomerulopathies.

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INTRODUCTION

Proteinuria is an early sign of glomerular diseases and its quantification for the initial evaluation and follow-up of patients with glomerulonephritis (GN) is routine in clinical practice. It is not only indispensable in making a diagnosis but is also used in monitoring the treatment response of kidney diseases. In fact, remission of proteinuria in some glomerular diseases represents the most powerful predictive factor for ultimate clinical outcomes[1,2]. In some clinical settings, such as nephrotic syndrome, its magnitude directly reflects the disease activity. As protein excretion varies during the course of a day, its estimation in 24-h urine collection is the gold standard method for the evaluation of proteinuria, but this method is cumbersome, time-consuming, more expensive, uncomfortable to the patient, and prone to errors due to under-collection or over-collection of multiple voided samples in a time-dependent manner. Moreover, it cannot be performed in some groups of patients such as children, the elderly, and physically and mentally disabled patients[3-5]. Since 1983, when Ginsberg *et al*[6] used the ratio as an alternative to 24-h proteinuria, many studies have been carried out using protein-to-creatinine ratios (PCRs) in spot or single-voided urine samples in different clinical settings to correlate these results with 24-h proteinuria, with a correlation ranging from 0.6-0.9 in different studies[7-10]. However, urinary PCR (uPCR) is also influenced by certain features like age, sex, race, muscle mass, and the timing of the urine sample. A sole reliance on uPCR to start or defer specific immunosuppressive treatment without considering these features may be inappropriate. Low muscle mass in the South Asian population has been shown to be an important determinant of low creatinine excretion[11-17]. This is particularly true in elderly, females, and malnourished patients. All these conditions will cause a relatively high uPCR for the same degree of proteinuria.

The correlation between the above two methods of estimation of proteinuria is also influenced by types of renal disease, degree of deterioration in kidney function and degree of proteinuria. Weak correlation is observed in cases of severe kidney failure, interstitial nephritis or severe proteinuria[3-5].

There are very few studies from Pakistan comparing uPCR with 24-h urine protein excretion and only one was done in patients with normal glomerular filtration rate[13,14]. An excellent correlation ($r = 0.96$) was found between random uPCR and standard 24-h urinary protein excretion in these patients ($P < 0.001$)[13]. However, the difference between

uPCR and 24-h protein excretion was not reported.

The objective of this study was to compare estimated protein excretion by uPCR with measured 24-h urine protein excretion in patients with different types of glomerulopathies at a single center in Pakistan.

MATERIALS AND METHODS

This cross-sectional and observational study was conducted at the outpatient clinic of the Department of Nephrology, Sindh Institute of Urology and Transplantation between 28th September 2017 and 28th March 2018. Eligibility for the study were adult subjects with the suspected glomerular disease with dipstick-positive proteinuria on the day of recruitment. Consecutive patients who agreed to submit a 24-h urine sample, who were more than 18 years old, and who were not diabetic were included. Exclusion criteria were chronic kidney disease stage 5 based on the Cockcroft-Gault formula, urinary tract infection, and those deemed incapable of collecting 24-h urine.

All patients were informed about the study's purpose and written consent was obtained. Patients were given detailed advice regarding 24-h urine collection from morning to the next morning. A wide-mouthed container was provided to every patient for collecting the 24-h urine. Patients were asked to collect the 24-h urine of their most convenient day and bring it on the day of completion. A spot urine sample was taken on the submission day for measuring the uPCR. A blood sample was taken at the same time. All samples were transported to the laboratory immediately. Serum creatinine and urinary creatinine (mg/dL) concentrations were determined using the modified Jaffe's method on an auto-analyzer. Creatinine clearance was calculated by the standard formula. Urinary protein concentration was determined with the colorimetric method using pyrogallol red. To assess the completeness of the collection, creatinine excretion in a 24-h urine sample was used. Specimens with creatinine excretion of 15-25 mg/kg in males, and 12-20 mg/kg in females, were considered adequate. Patients with creatinine excretion outside these ranges were excluded from the study.

The statistical analysis for this research was done by using SPSS version 22.0 (IBM Corp, Armonk, NY, United States). mean $\pm$ SD were evaluated for continuous data such as age, weight, height, body mass index (BMI), 24-h urinary volume, urinary protein excretion, serum creatinine, creatinine clearance, and spot uPCR. For categorical data such as gender, the frequency and percentages were calculated. Correlation between spot uPCR and 24-h urinary protein excretion was carried out using Pearson's correlation coefficient (r). P -value ≤ 0.05 was taken as significant. Bland and Altman plot was drawn using the average of protein excretion by both the methods on the X-axis and the difference between 24-h urinary protein and spot uPCR on the Y-axis. Mean bias and 95% confidence limits for the degree of agreement between the two methods were also calculated.

RESULTS

The main demographic, clinical and laboratory characteristics of the study population ($n = 157$) are shown in Table 1. The mean age of all patients was 30.45 ± 12.11 years. There were 94 (59.8%) males and 63 (40.2%) females. The majority of the patients ($n = 133$, 74.53 %) had a BMI of < 25 kg/m². The mean values of urinary protein excretion by both methods were similar to each other, with maximum values of protein excretion by both being less than 10 g/24 h. The mean 24-h urinary creatinine excretion was 834.96 ± 391.43 mg/24 h. The histopathological results of kidney biopsies in these patients are also shown in Table 1. It is apparent that focal segmental glomerulosclerosis and membranous GN were the two most common lesions followed by a variety of less common other pathological lesions. A positive, fair, and significant correlation between spot uPCR and 24-h urinary protein excretion ($r = 0.342$, P -value < 0.001) in the entire group (Figure 1). On subgroup analysis, a slightly better correlation was found in patients older than 47 years, and those with BMI > 25 kg/m² (Table 2).

Bland and Altman's plot comparing the differences between spot uPCR and 24-h protein measurement is depicted in Figure 2. The mean bias was 373 mg; however, the limits of agreement were fairly wide (from -3682 to 4069 mg). The scatter of differences increased as the amount of proteinuria increased. The mean bias and limits of agreement in the groups with less than and more than 3000 mg protein excretion are shown in Figures 3 and 4, respectively. Briefly, the mean bias was -93.64 mg and the limits of agreement were -2861.53 to 2674.25 mg in the group of patients with less than 3000 mg of proteinuria. These values were 158.36 and -4738.46 to 5035.18 mg in the group of patients with more than 3000 mg of proteinuria. As is obvious, the limits are wider with increasing levels of proteinuria.

DISCUSSION

The quantification of proteinuria is an important investigation in patients with various glomerular diseases. It not only helps in making a diagnosis but also helps in follow-up to monitor disease progression, and often, important therapeutic decisions are made based on its exact value. The traditional reference method, 24-h urine protein measurement, is a cumbersome and tedious test, and therefore spot uPCR has replaced it in clinical practice due to its simplicity, convenience, and presumed accuracy. Initial studies focused more on the correlation between the two methods and not surprisingly a moderate to strong correlation (0.57 to 0.9) was reported in different studies[1-5].

In the present study, a fair correlation of spot uPCR with 24-h urinary protein measurement was observed. Although this was statistically significant, it is lower than the previously described correlation in many other studies[1-5,7-10,18-

Table 1 The main demographic, clinical, laboratory, and pathology characteristics of the study population (157)

Parameters	Values
Age (yr)	30.45 ± 12.108
Weight (kg)	59.70 ± 15.067
Height (cm)	163.98 ± 11.476
Body mass index (kg/m ²)	22.30 ± 5.65
Serum creatinine (mg/dL)	1.00 ± 0.54
24-h urinary creatinine (mg/24-h)	834.12 ± 391.43
Creatinine clearance (ml/min)	75.05 ± 33.55
Spot urine protein (mg/dL)	296.04 ± 159.65
Spot urine creatinine (mg/dL)	108.83 ± 58.01
24-h urine protein excretion (mg/24-h)	3192.78 ± 1959.79
Spot urine protein to creatinine ratio (mg/mg)	3.15 ± 1.52
24-h urine volume	1711.40 ± 882.03
Histopathological diagnosis, n (%)	
Focal segmental glomerulosclerosis	52 (33.12)
Membranous glomerulonephritis	44 (28)
Mesangiocapillary glomerulonephritis	28 (17.83)
IgM nephropathy	11 (7)
Lupus nephritis	10 (6.36)
Minimal change disease	4 (2.54)
Others	8 (5.09)

All values are in mean ± SD, unless otherwise specified.

Table 2 Correlation of spot urine protein-to-creatinine ratio with 24-h urinary protein estimation stratified according to age and body mass index

Parameters	No of patients (n)	Correlation coefficient (r)	P value
Age (yr) groups			
34-46	35	0.475	0.004
> 47	21	0.780	0.001
BMI (kg/m ²) ranges			
23-25	24	0.411	0.046
> 25	40	0.459	0.00
Proteinuria			
< 3000 mg/d	79	0.021	0.28
≥ 3000 mg/d	78	0.216	0.058

BMI: Body mass index.

21]. These results are not entirely explained on the basis of extremes of proteinuria in our population. The median protein excretion in our population was 2970 mg in 24 h, and we, therefore, stratified them according to proteinuria above and below 3000 mg to see if the correlation changes, as most of the therapeutic decisions are taken when proteinuria is above 3000 mg. There was an equal number of patients in the two groups (79 in < 3000 mg group, and 78 in ≥ 3000 mg group). The correlation was much weaker in the group with protein excretion of less than 3000 mg and failed to reach statistical significance. In the group with protein excretion of more than 3000 mg in 24 h, the correlation with spot uPCR was just

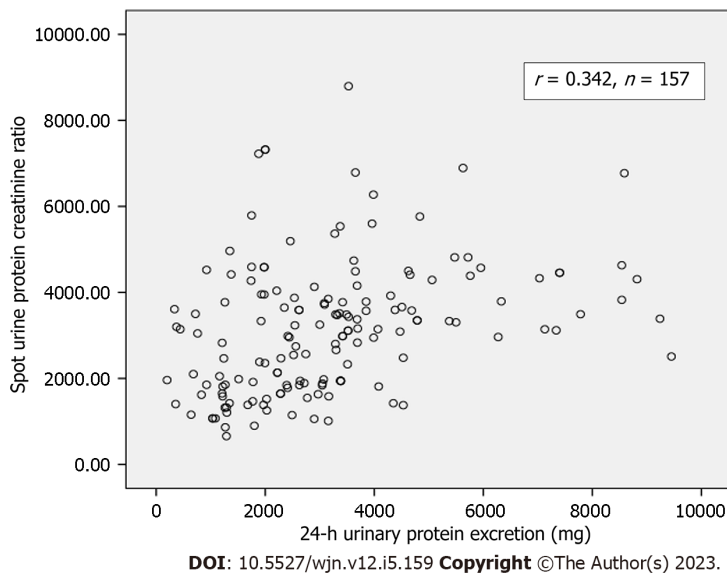


Figure 1 Correlation between spot urine protein-to-creatinine ratio and 24-h urinary protein excretion in all patients ($n = 157$).

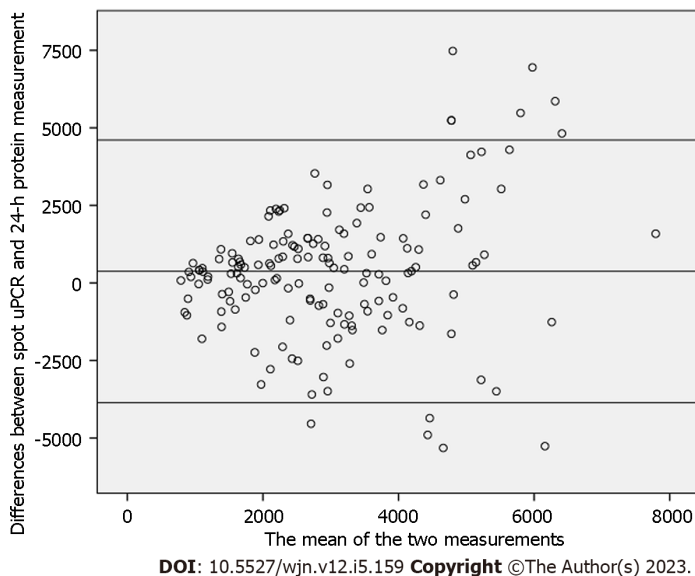


Figure 2 Bland and Altman plot comparing the differences between spot urine protein-to-creatinine ratio and 24-h protein measurement against the mean of the measurement by the two methods. The mean bias is 373 mg; however, the limits of agreement are fairly wide (from -3682 to 4069 mg), particularly as the mean of the two methods rises.

significant ($P = 0.058$). There were 13 patients in our group who had protein excretion in excess of 6000 mg and after excluding them from the group of 78 patients with protein excretion ≥ 3000 mg, the correlation with spot uPCR ($r = 0.295$) became significant ($P = 0.02$). Similarly, there were 12 patients in the group with protein excretion < 3000 mg who had proteinuria of less than 1000 mg, and after excluding them from this group, when we recalculated the correlation with spot uPCR it remained weak ($r = 0.21$).

As is well known, uPCR is also influenced by gender, as females have lower creatinine excretion due to lower muscle mass and this can give rise to a higher ratio compared to males for a similar degree of proteinuria. However, the correlation was not much different when we stratified the entire group according to gender. Besides the degree of proteinuria and gender, uPCR is also influenced by renal function, the timing of random (spot) urine specimens, and the handling of urine samples[10,11]. The mean creatinine clearance in this study population was 75 mL/minute, and 75% of the population had serum creatinine less than 1.23 mg/dL; therefore it is unlikely that the ratio was influenced by compromised renal functions. Patients were asked to submit spot urine samples on the following day of 24-h urine collection, but this sample was taken at different times of day in individual patients and physical activity may have influenced protein excretion in some patients who had come late for submitting their specimens.

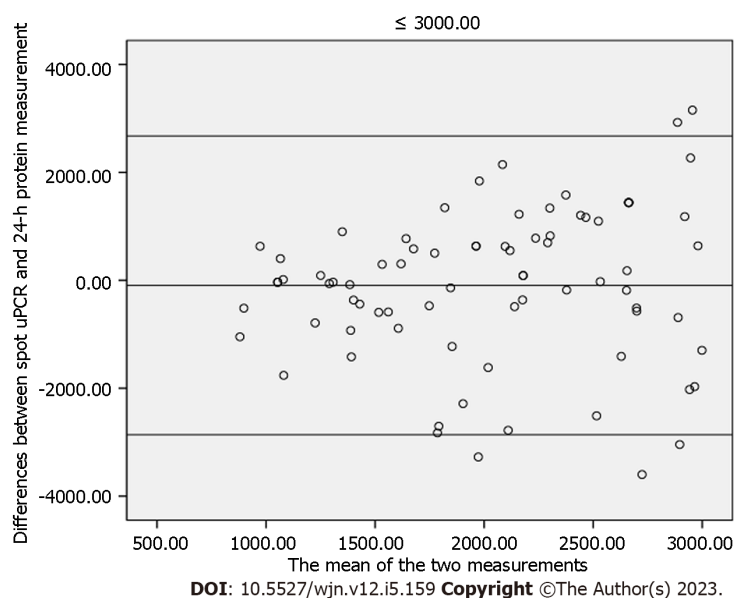


Figure 3 The mean bias and limits of agreement in the group of patients with protein excretion of less than 3000 mg. The mean bias is -93.64 mg and the limits of agreement are -2861.53 to 2674.25 mg in this group of patients.

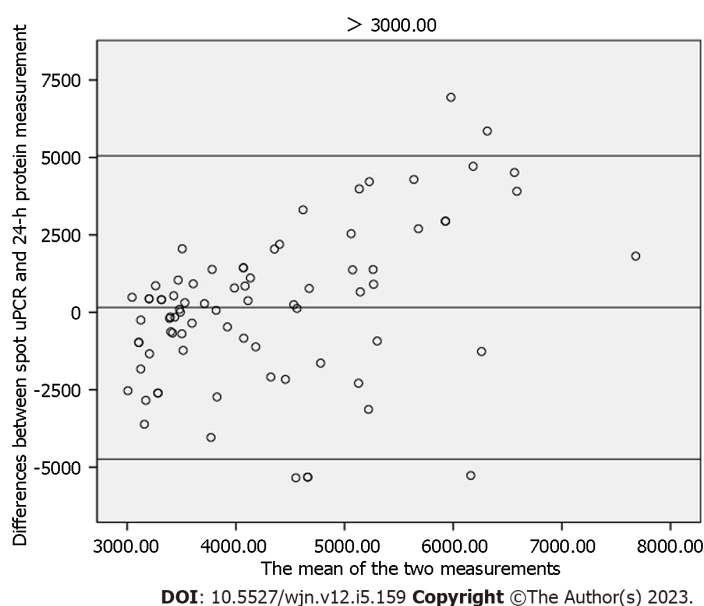


Figure 4 The mean bias and limits of agreement in the group of patients with more than 3000 mg protein excretion. The mean bias is 158.36 mg and the limits of agreement are -4738.46 to 5035.18 mg in this group of patients.

One possible explanation for the poor correlation between uPCR and 24-h urinary protein measurement is that the latter assumes a creatinine excretion of 1000 mg/d which may be incorrect in some populations[6]. Around 50% of our population had a BMI of < 21.5 kg/m² suggesting low muscle mass and hence low creatinine excretion. Indeed, when we analyzed the correlation between spot uPCR and 24-h urine protein excretion in the group of patients with BMI >25 kg/m², we observed a much stronger correlation than patients with lower BMI ($r = 0.45$, $P = 0.003$).

More important than correlation from the clinical perspective is the degree of agreement or the difference between two measurements. To replace 24-h measurement with uPCR in spot urine samples for clinical decision-making, it is prudent to see whether the two techniques agree sufficiently. In this study, the limits of agreement were fairly wide, more so with higher grades of proteinuria. Irrespective of the fact that whether proteinuria was sub-nephrotic or in the nephrotic range, these differences are unacceptable. In an earlier study of 170 proteinuric patients, good agreement between the two methods was reported in the range between 200 mg and 3.5 g protein excretion[22]. A meta-analysis of 13 studies in patients with systemic lupus erythematosus showed poor agreement between the two methods[23]. In a study using NEPTUNE cohort of patients, there was modest correlation between the two methods, and both correlation and predictability improved on Log10 transformation of values[24]. Only 25% of patients in NEPTUNE cohort had nephrotic syndrome, making it difficult to generalize it for higher grades of proteinuria. Lately, in a single center study of 142

proteinuric patients, a poor agreement was reported between 24-h urine protein excretion and uPCR from different timed spot samples. The limits of agreement were widest when protein excretion exceeded 3.5 g in 24 h (-3.2 to 8.2)[25].

Our study has certain limitations. It is a single center and single laboratory-based study. We used uPCR rather than albumin: Creatinine ratio, which is more reliable compared to uPCR. Spot urine samples were taken at different times of day in individual patients which may have affected protein excretion and hence its concentration. Some patients were already on steroids, which causes sarcopenia and decreases creatinine excretion resulting in higher uPCR. Moreover, specific disease diagnoses were not recorded in this study. Some of the patients might have had non-glomerular pathology. The main strength of our study is the broad range of proteinuria used for comparison, with a nearly equal number of patients below and above the nephrotic threshold of proteinuria. The spot urine sample was collected on the very next day of 24-h urine collection so that both represented similar pathophysiology. Although 24-h urine protein excretion is considered the gold standard test for accurate estimation of proteinuria, over-collection and under-collection of urine sample affects its accuracy[26-28]. We tried to mitigate this issue by excluding patients who had creatinine excretion outside the expected range based on their weight.

CONCLUSION

In conclusion, considering the overall poor correlation and the wide limits of agreement between 24-h urine protein excretion and uPCR, the latter should be used with great caution to predict protein excretion in patients with glomerular disease. This is more so when important therapeutic decisions are being made based on the degree of proteinuria.

ARTICLE HIGHLIGHTS

Research background

There are a number of methods by which the quantification of protein excretion in urine is done to inform clinical decisions. Among these, the estimation of protein excretion in the 24-h urinary sample is the traditional and gold standard method. However, it is cumbersome, time-consuming, and prone to errors. The alternative method of measuring urine protein-to-creatinine ratio (uPCR) is used widely in clinical practice as it is quick, patient-friendly, and reliable. The available data on the correlation between the above two methods is controversial.

Research motivation

We also heavily rely on uPCR for our routine patient care. However, we do not know how it correlates with 24-h urinary protein excretion. This motivated us to determine the correlation and degree of agreement between the two tests, so that we should use uPCR results accordingly.

Research objectives

The objectives of this study were to determine the correlation of spot uPCR with 24-h urinary protein excretion test and in particular, the degree of agreement between the two tests, in patients suffering from various forms of glomerulopathies so that we may use this test with caution in future.

Research methods

This was a cross-sectional, observational study conducted on all newly presenting adult patients (age: 18 to 60 years) with proteinuria who were being investigated for suspected glomerulonephritis (GN). All patients were counseled regarding 24-h urine collection. A spot urine sample was collected the next day at the time of submission of a 24-h urine sample for measuring uPCR along with a blood sample. SPSS version 20.0 was used for statistical analysis.

Research results

A total of 157 patients with a mean age of 30.45 ± 12.11 years were included. There were 94 (59.8%) males and 63 (40.2%) females. The mean 24-h urinary protein excretion was 3192.78 ± 1959.79 mg and the mean spot uPCR was 3.16 ± 1.52 in all patients. A significant but poor correlation was observed between spot uPCR and 24-h urinary protein excretion ($r = 0.342$, $P = 0.01$) among all patients. On subgroup analysis, a slightly better correlation was found in patients older than 47 years ($r = 0.78$), and those with body mass index $> 25 \text{ kg/m}^2$ ($r = 0.45$). Bland and Altman's plot analysis of the two tests also showed a wide range of the limits of agreement between the two methods.

Research conclusions

The results from this study show a significant, positive but poor correlation between spot uPCR and 24-h urinary protein estimation in various types of glomerular diseases. The agreement between the two methods was also poor. Hence, there is a need for careful interpretation of the ratio in an unselected group of patients with glomerular diseases.

Research perspectives

There is a need to conduct a well-planned, international, multi-center study to resolve the controversy of correlation and agreement between the two most widely used methods of proteinuria estimation in clinical practice.

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FOOTNOTES

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Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: The dataset and related documents are available from the corresponding author at [dramber88@gmail.com]. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Observational Study

Antihypertensive prescribing patterns in non-dialysis dependent chronic kidney disease: Findings from the Salford Kidney Study

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Abstract

BACKGROUND

Hypertension is commonly observed in patients living with chronic kidney disease (CKD). Finding an optimal treatment regime remains challenging due to the complex bidirectional cause-and-effect relationship between hypertension and CKD. There remains variability in antihypertensive treatment practices.

AIM

To analyze data from the Salford Kidney Study database in relation to antihypertensive prescribing patterns amongst CKD patients.

METHODS

The Salford Kidney Study is an ongoing prospective study that has been recruiting CKD patients since 2002. All patients are followed up annually, and their medical records including the list of medications are updated until they reach study endpoints [starting on renal replacement therapy or reaching estimated glomerular filtration rate (eGFR) expressed as mL/min/1.73 m² ≤ 10 mL/min/1.73 m², or the last follow-up date, or data lock on December 31, 2021, or death]. Data on antihypertensive prescription practices in correspondence to baseline eGFR, urine albumin-creatinine ratio, primary CKD aetiology, and cardiovascular disease were evaluated. Associations between patients who were

prescribed three or more antihypertensive agents and their clinical outcomes were studied by Cox regression analysis. Kaplan-Meier analysis demonstrated differences in survival probabilities.

RESULTS

Three thousand two hundred and thirty non-dialysis-dependent CKD patients with data collected between October 2002 and December 2019 were included. The median age was 65 years. A greater proportion of patients were taking three or more antihypertensive agents with advancing CKD stages (53% of $\text{eGFR} \leq 15 \text{ mL/min/1.73 m}^2$ vs 26% of $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$, $P < 0.001$). An increased number of patients receiving more classes of antihypertensive agents was observed as the urine albumin-creatinine ratio category increased (category A3: 62% vs category A1: 40%, $P < 0.001$), with the upward trends particularly noticeable in the number of individuals prescribed renin angiotensin system blockers. The prescription of three or more antihypertensive agents was associated with all-cause mortality, independent of blood pressure control (hazard ratio: 1.15; 95% confidence interval: 1.04-1.27, $P = 0.006$). Kaplan-Meier analysis illustrated significant differences in survival outcomes between patients with three or more and those with less than three antihypertensive agents prescribed (log-rank, $P < 0.001$).

CONCLUSION

Antihypertensive prescribing patterns in the Salford Kidney Study based on CKD stage were consistent with expectations from the current United Kingdom National Institute of Health and Care Excellence guideline algorithm. Outcomes were poorer in patients with poor blood pressure control despite being on multiple antihypertensive agents. Continued research is required to bridge remaining variations in hypertension treatment practices worldwide.

Key Words: Hypertension; Chronic kidney disease; Antihypertensive agents; Prescribing patterns; Cardiovascular complications; Renin angiotensin system blockers

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Core Tip: This is an observational study that prospectively evaluated antihypertensive prescribing patterns in 3230 non-dialysis chronic kidney disease (CKD) patients over a 20-year period. Antihypertensive prescribing patterns based on CKD stage were consistent with expectations from the United Kingdom National Institute of Health and Care Excellence guideline algorithm and other international guidelines in relation to hypertension management in CKD.

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INTRODUCTION

Chronic kidney disease (CKD) is a progressive disease defined by the presence of structural or functional abnormalities within the kidney for 3 mo or more according to the Kidney Disease Improving Global Outcomes (KDIGO)[1]. Touted as an emerging public health issue of the 21st century, the prevalence of CKD is exponentially growing and is projected to become the fifth-leading cause of mortality globally by 2040[2]. The aetiology of CKD is multidimensional and complex, of which there are various causes and consequences[3-5]. Other than diabetes mellitus, hypertension is a major contributor towards the progression of CKD and a leading consequence of CKD[6]. Depending on the stage of CKD, the prevalence of hypertension in CKD populations varies (ranging between 67% and 92%, according to previously published data), but the majority of patients with CKD are likely to have hypertension[7,8]. Given the potential health consequences of hypertension over time, namely its associated cardiovascular risks and risk of further kidney damage, adequate control of blood pressure (BP) in the CKD population is of vital importance to improve clinical outcomes[9,10].

It is not known to what extent clinicians adopt guideline-recommended or preferred antihypertensive treatment approaches for their CKD patients in the real-world setting[7,11]. Previous electronic health record and prospective longitudinal studies noted clinicians primarily prescribed angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for CKD patients with hypertension, but varying combinations of antihypertensive prescription over time was noted when all antihypertensive agents are considered[12-16]. It remains largely unestablished which combination(s) of antihypertensive agents would generate the best results in terms of BP control and other clinical outcomes. Aiming to address these unknowns, our study evaluated trends and patterns relating to antihypertensive prescription over a 20-year period in patients identified with non-dialysis-dependent CKD included in the Salford Kidney Study (SKS).

MATERIALS AND METHODS

Study cohort

Our investigation was conducted on patients enrolled in the non-dialysis-dependent CKD arm of the SKS (SKS-CKD). The SKS-CKD is an ongoing long-term prospective observational study that has been recruiting patients with CKD since the year 2002. Details of study recruitment in the SKS have been described in previously published literature[17,18]. In brief, any CKD patient above the age of 18 years and able to provide informed consent is recruited. At study baseline (*i.e.* date of recruitment), data including demographic information, comorbidities, physical parameters (weight, height, BP, heart rate, *etc*) and a detailed medication history is recorded. The patients are then followed up annually to update their comorbidity status and medication list until they reach a study endpoint [which may include death, starting on renal replacement therapy (RRT), reaching estimated glomerular filtration rate (eGFR) ≤ 10 mL/min/1.73 m², the last follow-up date, or data lock of December 31, 2021 for this study]. All haematological and biochemical variables at study and routine clinic visits are recorded from electronic patient records.

Study definitions

In the SKS, hypertensive status was defined as being on antihypertensive agents or recorded as having a history of hypertension in general practitioner records. A smoking history was defined as current or past history of smoking, and a similar definition was followed in the collection of alcohol history. Body mass index was calculated using weight in kilograms and height in meters (kg/m²). End stage kidney disease (ESKD) was defined as starting on RRT or reaching an eGFR ≤ 10 mL/min/1.73 m² for patients who opted for conservative care. We defined renin angiotensin system (RAS) blockers as being ACEI or ARB or renin inhibitors.

Data and statistical analysis

The baseline characteristics of the cohort were grouped based on CKD stages (categorized by eGFR) and proteinuria [categorized by urine albumin-creatinine ratio (uACR)]. uACR was calculated from urine protein-creatinine ratio (uPCR). This involved initial conversion from mg/mmol to mg/g by multiplication of 8.84, and further conversion from uPCR (uPCR: the standard measure in this real world population) to uACR as per the standardized formula in the kidney failure risk equation[19].

Prescription patterns of antihypertensive agents at baseline were presented corresponding to eGFR categories, uACR categories, primary kidney disease aetiology, and cardiovascular disease. Antihypertensive agent(s) prescribing trends were also examined at the 12-mo and 24-mo follow-up.

When presenting results from our statistical analyses, continuous variables were expressed with the median value (interquartile range). After checking for the normality of distribution, the *P* value was calculated by the Kruskal-Wallis H test. Categorical variables are expressed as frequencies in absolute number form (percentage), with *P* values calculated by the χ^2 test. The association between being prescribed three or more antihypertensive agents and clinical outcomes (*i.e.* all-cause mortality and reaching ESKD) was studied by univariate and multivariate Cox regression analysis. The multivariable models were developed by including variables in a stepwise manner. Kaplan-Meier analysis was used to demonstrate the differences in survival probabilities, with the log-rank test used to calculate the *P* values. The annual rate of decline in eGFR (delta eGFR) was calculated using all available eGFRs between the study baseline and endpoints by linear regression analysis. Only patients with three or more eGFRs and at least 1 year of follow-up data were included in the delta eGFR analysis. All statistical analyses were performed using IBM SPSS Version 26, registered with the University of Manchester.

Ethical considerations

The SKS received ethical approval for all of the observational studies conducted in relation to its database, with individual patient consent. The research ethics number is 15/NW/0818.

RESULTS

Baseline characteristics

A total of 3230 patients with complete datasets were included in this analysis. The median age of the cohort was 65 years with a predominance of the male sex (60%) and those of white ethnicity (96%). At baseline, the majority of study participants (66%) had an eGFR between 15 and 45 mL/min/1.73 m². As baseline eGFR declined, the median systolic BP of the cohort was noted to have increased, and a higher proportion of those with lower eGFR also had a history of hypertension, diabetes, and cardiovascular events (*P* < 0.001). Biochemical variables showed decreases in haemoglobin and calcium levels and increases in phosphate levels in correspondence to worsening eGFR (*P* < 0.001) (Table 1).

Distribution of antihypertensive agent prescription practices based on eGFR and primary kidney disease aetiology

Amongst patient groups with a lower eGFR, there were greater proportions that were receiving three or more antihypertensive agents (53% of eGFR ≤ 15 mL/min/1.73 m² vs 26% of eGFR ≥ 60 mL/min/1.73 m², *P* < 0.001). The most prescribed antihypertensive agents were RAS blockers (61%), followed by diuretics (47%), dihydropyridine calcium channel blockers (CCB) (39%), and beta blockers (34%). Alpha-blockers were also a popularly prescribed antihypertensive and prescribed more frequently in lower eGFR ranges. The proportion of patients receiving RAS blockers decreased with a lower eGFR,

Table 1 Demographic information and baseline characteristics of the cohort based on estimated glomerular filtration rate categories

Demographic variables	eGFR $\geq$ 60, n = 218 ¹	eGFR 45-59, n = 491 ¹	eGFR 30-45, n = 962 ¹	eGFR 15-29, n = 1174 ¹	eGFR < 15, n = 385 ¹	Total, n = 3230 ¹	P value ¹
Age, yr	53 (44-63)	62 (50-70)	68 (56-75)	70 (60-78)	71 (60-78)	67 (56-76)	< 0.001
Sex, male	126 (57.8)	308 (62.7)	573 (59.6)	691 (58.9)	251 (65.2)	1949 (60.3)	0.143
Ethnicity, white	198 (90.8)	467 (95.1)	924 (99.6)	1127 (96.0)	375 (97.4)	3091 (95.7)	0.003
BMI, kg/m ²	28.3 (24.6-33.2)	28.2 (25.0-32.4)	28.0 (25.0-32.4)	28.0 (25.0-32.6)	27.4 (24.0-33.0)	28.0 (24.7-32.6)	0.490
Systolic BP, mmHg	132 (120-148)	135 (122-150)	139 (125-153)	140 (126-155)	143 (130-160)	139 (125-154)	< 0.001
Diastolic BP, mmHg	76 (70-82)	76 (68-82)	75 (67-81)	72 (65-80)	75 (66-82)	75 (66-81)	0.001
Smoking history	124 (56.9)	300 (61.1)	630 (65.5)	781 (65.5)	255 (66.2)	2090 (64.7)	0.027
Alcohol history	121 (55.5)	252 (51.3)	465 (48.3)	504 (42.9)	149 (38.7)	1491 (46.2)	< 0.001
Hypertension	166 (76.1)	414 (84.3)	862 (89.6)	1091 (92.9)	362 (94.0)	2895 (89.6)	< 0.001
Diabetes mellitus	37 (17.0)	109 (22.2)	291 (30.2)	456 (38.8)	148 (38.4)	1041 (32.2)	< 0.001
IHD	21 (9.6)	75 (15.3)	221 (23.0)	275 (23.4)	75 (19.5)	667 (20.7)	< 0.001
MI	14 (6.4)	61 (12.4)	149 (15.5)	199 (17.0)	59 (15.3)	482 (14.9)	0.001
CCF	18 (8.3)	52 (10.6)	169 (17.6)	233 (19.8)	84 (21.8)	556 (17.2)	< 0.001
CVA	8 (3.7)	25 (5.1)	75 (7.8)	100 (8.5)	41 (10.6)	249 (7.7)	0.004
PVD	19 (8.7)	47 (9.6)	122 (12.7)	169 (14.4)	58 (15.1)	415 (12.8)	0.016
COPD	32 (14.7)	74 (15.1)	179 (18.6)	219 (18.7)	64 (16.6)	568 (17.6)	0.260
CLD	8 (3.7)	19 (3.9)	30 (3.1)	33 (2.8)	9 (2.3)	99 (3.1)	0.683
Malignancy	19 (8.7)	39 (7.9)	109 (11.3)	136 (11.6)	50 (13.0)	353 (10.9)	0.094
Laboratory variables							
Haemoglobin, g/L	134 (121-145)	131 (120-141)	126 (115-137)	120 (110-130)	113 (104-122)	123 (112-135)	< 0.001
Albumin, g/L	44 (41-46)	43 (41-45)	43 (40-45)	42 (40-44)	42 (39-44)	43 (40-45)	< 0.001
Corrected calcium, mmol/L	2.32 (2.22-2.40)	2.33 (2.24-2.41)	2.31 (2.23-2.39)	2.30 (2.20-2.39)	2.28 (2.17-2.37)	2.31 (2.22-2.39)	< 0.001
Phosphate, mmol/L	1.05 (0.91-1.10)	1.03 (0.91-1.16)	1.07 (0.95-1.21)	1.16 (1.02-1.31)	1.39 (1.21-1.59)	1.12 (0.98-1.29)	< 0.001
ALP, U/L	71 (57-85)	76 (59-97)	82 (66-102)	86 (69-112)	89 (69-111)	83 (66-105)	< 0.001
uACR, mg/g ²	15.9 (8.3-57.2)	21.0 (10.6-60.5)	24.0 (11.7-77.0)	43.0 (16.4-132.7)	106.5 (44.4-232.6)	32.7 (13.4-111.1)	< 0.001

¹Continuous variables are expressed with the median value (interquartile range). The *P* values were calculated by the Kruskal Wallis H test. Categorical variables are expressed as numbers (percentage). The *P* values were calculated by the χ^2 test.

²Missing urine albumin-creatinine ratio values for 391 patients.

ALP: Alkaline phosphatase; BMI: Body mass index; BP: Blood pressure; CCF: Congestive cardiac failure; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular accidents; eGFR: Estimated glomerular filtration rate expressed as mL/min/1.73 m²; IHD: Ischemic heart disease; MI: Myocardial infarction; PVD: Peripheral vascular disease; uACR: Urine albumin-creatinine ratio.

whereas the proportion on diuretics, dihydropyridine CCBs, and beta blockers increased (*P* < 0.001) (Table 2).

Furthermore, the distribution of antihypertensive agent prescriptions for patients across the spectrum of primary kidney disease aetiologies illustrated that RAS blockers were the predominant agents for most diagnoses, followed by diuretics and dihydropyridine CCBs (Table 3).

Distribution of antihypertensive agent prescription practices based on uACR and cardiovascular comorbidity

A greater proportion of patients were receiving three or more antihypertensive agents with each higher uACR category (category A1: 40% *vs* category A2: 43% *vs* category A3: 62%, *P* < 0.001). There was a trend of increased numbers of individuals prescribed ACEI or ARB (Table 4).

When comparing between patients with and without a history of congestive cardiac failure (CCF), diuretics (68% *vs* 43%, *P* < 0.001), potassium-sparing diuretics (spironolactone or eplerenone) (10% *vs* 2%, *P* < 0.001), and beta blockers (45% *vs* 32%, *P* < 0.001) were prescribed more frequently amongst those diagnosed with CCF. Similar prescription patterns were noted for any other form of cardiovascular disease. Interestingly, there were no significant differences in the pattern of prescription of RAS blockers alone, based on cardiovascular disease status (Table 5).

Table 2 Number of patients prescribed each antihypertensive class at baseline, organized by estimated glomerular filtration rate categories at baseline

Antihypertensive class	eGFR > 60, n = 218 ¹	eGFR 45-59, n = 491 ¹	eGFR 30-45, n = 962 ¹	eGFR 15-29, n = 1174 ¹	eGFR < 15, n = 385 ¹	Total, n = 3230 ¹	P value ¹
None	54 (24.8)	73 (14.9)	97 (10.1)	78 (6.6)	26 (6.8)	328 (10.2)	< 0.001
Three or more agents	57 (26.1)	158 (32.2)	397 (41.3)	565 (48.1)	206 (53.5)	1383 (42.8)	< 0.001
Diuretic (thiazide and loop)	58 (26.6)	172 (35.0)	441 (45.8)	641 (54.6)	213 (55.3)	1525 (47.2)	< 0.001
CCB (dihydropyridine)	58 (26.6)	149 (30.3)	364 (37.8)	480 (40.9)	205 (53.2)	1256 (38.9)	< 0.001
CCB (non-dihydropyridine)	6 (2.8)	11 (2.2)	44 (4.6)	50 (4.3)	23 (6.0)	134 (4.1)	0.055
Beta-blocker	51 (23.4)	133 (27.1)	324 (33.7)	443 (37.7)	156 (40.5)	1107 (34.3)	< 0.001
Alpha-blocker	28 (12.8)	72 (14.7)	186 (19.3)	335 (28.5)	158 (41.0)	779 (24.1)	< 0.001
Central agents	9 (4.1)	15 (3.1)	34 (3.5)	59 (5.0)	33 (8.6)	150 (4.6)	0.001
Vasodilators	2 (0.9)	2 (0.4)	6 (0.6)	13 (1.1)	7 (1.8)	30 (0.9)	0.189
RAS blocker	126 (57.8)	316 (64.4)	616 (64.0)	733 (62.4)	192 (50.0)	1983 (61.4)	< 0.001
Dual RAS blockers	22 (10.1)	34 (7.0)	50 (5.2)	67 (5.7)	14 (3.6)	187 (5.8)	0.014
Spirinolactone/eplerenone	7 (3.2)	17 (3.5)	36 (3.7)	44 (3.7)	8 (2.1)	112 (3.5)	0.599

¹Absolute number for frequencies (percentage). The P values were calculated by the χ^2 test.

CCB: Calcium channel blocker; eGFR: estimated glomerular filtration rate expressed as mL/min/1.73 m²; RAS: Renin angiotensin system.

Table 3 Number of patients prescribed each antihypertensive class at baseline, organised by primary aetiology of chronic kidney disease at baseline

Primary aetiology of CKD	Three or more ¹	RAS blocker ¹	Diuretic ¹	Beta blocker ¹	Alpha blocker ¹	CCB (dihydropyridine) ¹	CCB (non-dihydropyridine) ¹	Central agents ¹
Diabetes, n = 636	386 (61)	463 (73)	416 (65)	239 (38)	220 (35)	281 (44)	32 (5)	53 (8)
Hypertension, n = 471	246 (52)	294 (62)	245 (52)	210 (45)	154 (33)	222 (47)	33 (7)	21 (5)
Renovascular disease, n = 256	163 (64)	142 (56)	178 (70)	121 (47)	92 (36)	122 (48)	20 (8)	27 (11)
Pyelonephritis, n = 200	40 (20)	102 (51)	54 (27)	50 (25)	23 (12)	61 (31)	4 (2)	3 (2)
ADPKD, n = 197	66 (34)	149 (76)	69 (35)	55 (28)	40 (20)	78 (40)	2 (1)	6 (3)
Tubulointerstitial nephritis, n = 116	9 (8)	40 (35)	18 (16)	27 (23)	8 (7)	35 (30)	3 (3)	2 (20)
Glomerulonephritis, n = 375	171 (46)	305 (81)	174 (46)	95 (25)	73 (20)	147 (39)	9 (2)	21 (6)
Vasculitis, n = 118	31 (26)	61 (52)	34 (29)	35 (30)	19 (16)	40 (34)	2 (2)	1 (1)
Haematological disease, n = 31	8 (26)	14 (45)	9 (29)	8 (26)	4 (13)	7 (23)	0	1 (3)
Other/unknown aetiology, n = 830	263 (32)	413 (50)	328 (40)	267 (32)	146 (18)	263 (32)	29 (4)	15 (2)

¹Absolute number for frequencies (percentages).

ADPKD: Autosomal dominant polycystic kidney disease; CCB: Calcium channel blocker; CKD: Chronic kidney disease; RAS: Renin angiotensin system.

There were no significant differences in antihypertensive prescription patterns over the 12-mo and 24-mo follow-up period (Tables 6 and 7). Overall, there were more patients achieving BP < 140/90 mmHg at 12 mo (52% *vs* 48%, $P = 0.008$) and at 24 mo (51.7% *vs* 48%, $P = 0.015$) compared to baseline. However, when only patients on three or more agents over the 24-mo follow-up period were considered, there were no statistically significant results as to whether more patients achieved BP < 140/90 mmHg (Tables 8 and 9).

Table 4 Number of patients prescribed with each antihypertensive class at baseline, organized by urine albumin-creatinine ratio categories at baseline

Antihypertensive class	uACR < 30, n = 1355 ^{1,2}	uACR 30-300, n = 1236 ^{1,2}	uACR > 300, n = 248 ^{1,2}	Total, n = 2839 ^{1,3}	P value ¹
None	148 (10.9)	112 (9.1)	12 (4.8)	272 (9.6)	< 0.001
Three or more agents	547 (40.4)	530 (42.9)	155 (62.5)	1232 (43.4)	< 0.001
Diuretic (thiazide and loop)	656 (48.4)	542 (43.9)	148 (59.7)	1346 (47.4)	< 0.001
CCB (dihydropyridine)	477 (35.2)	516 (41.7)	122 (49.2)	1115 (39.3)	< 0.001
CCB (non- dihydropyridine)	61 (4.5)	54 (4.4)	11 (4.4)	126 (4.4)	0.987
Beta-blocker	458 (33.8)	418 (33.8)	93 (37.5)	969 (34.1)	0.504
Alpha blocker	265 (19.6)	335 (27.1)	87 (35.1)	687 (24.2)	< 0.001
Central agent	45 (3.3)	69 (5.6)	23 (9.3)	137 (4.8)	< 0.001
Vasodilator	11 (0.8)	16 (1.3)	1 (0.4)	28 (1.0)	0.288
RAS blocker	840 (62.0)	753 (61.0)	174 (70.2)	1767 (62.2)	0.023
Dual RAS blockers	49 (3.6)	80 (6.5)	41 (16.5)	170 (6.0)	< 0.001
Spironolactone/eplerenone	52 (3.8)	29 (2.3)	11 (4.4)	92 (3.2)	0.054

¹Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.

²uACR in mg/mg = $-0.171 + 0.780$ urine protein-creatinine ratio in mg/mg.

³Total was 2839 rather than 3230 as in previous tables as some patients were missing uACR data.

CCB: Calcium channel blocker; RAS: Renin angiotensin system; uACR: Urine albumin-creatinine ratio in mg/g.

Table 5 Number of patients prescribed with each antihypertensive class at baseline, organized by categories according to the prevalence of congestive cardiac failure and other cardiovascular events at baseline

Antihypertensive class	CCF, n = 556 ¹	No CCF, n = 2674 ¹	P value ¹	CVE, n = 1829 ¹	No CVE, n = 1401 ¹	P value ¹
None	22 (4.0)	306 (11.4)	< 0.001	72 (5.1)	256 (14.0)	< 0.001
Diuretic (thiazide and loop)	381 (68.4)	1144 (42.8)	< 0.001	818 (58.4)	707 (38.7)	< 0.001
CCB (dihydropyridine)	192 (34.5)	1064 (39.8)	0.021	561 (40.0)	695 (38.0)	0.238
CCB (non-dihydropyridine)	32 (5.8)	102 (3.8)	0.037	92 (6.6)	42 (2.3)	< 0.001
Beta blocker	248 (44.6)	859 (32.1)	< 0.001	621 (44.3)	486 (26.6)	< 0.001
Alpha blocker	140 (25.2)	639 (23.9)	0.520	385 (27.5)	394 (21.7)	< 0.001
Central agent	29 (5.2)	121 (4.5)	0.481	73 (5.2)	77 (4.2)	0.180
Vasodilator	4 (0.7)	26 (1.0)	0.572	17 (1.2)	13 (0.7)	0.140
RAS blocker	360 (64.7)	1623 (60.7)	0.074	839 (42.3)	1144 (57.7)	0.124
Dual RAS blockers	24 (4.3)	163 (6.1)	0.102	70 (37.4)	117 (62.6)	0.091
Spironolactone/eplerenone	56 (10.1)	56 (2.1)	< 0.001	80 (5.7)	32 (1.7)	< 0.001

¹Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.

CCB: Calcium channel blocker; CCF: Congestive cardiac failure; CVE: Cardiovascular events; RAS: Renin angiotensin system.

Associations between antihypertensive prescription patterns and clinical outcomes

In Cox regression models, the prescription of three or more antihypertensive agents was strongly associated with all-cause mortality (multivariate model 3: hazard ratio: 1.14; 95% confidence interval: 1.03-1.26, *P* = 0.008) (Table 10). A similar association was observed when the outcome considered was progression to ESKD (multivariate model 3: hazard ratio: 1.47; 95% confidence interval: 1.25-1.72, *P* < 0.001) (Table 11).

Kaplan-Meier analysis illustrated significant differences in survival outcomes (all-cause mortality and RRT-free survival) between patients receiving three or more compared to those with less than three antihypertensive agents prescribed (log-rank, *P* < 0.001) (Figures 1 and 2). Being on RAS blockers was associated with a higher survival (log-rank, *P* < 0.001) but demonstrated no differences in terms of reaching ESKD and requiring RRT (log-rank, *P* = 0.113) (Figures 3 and 4).

Table 6 Number of patients prescribed with each antihypertensive class at baseline and at the 12-mo follow-up

Antihypertensive class	Baseline, <i>n</i> = 2256 ¹	12-mo follow-up, <i>n</i> = 2256 ¹	<i>P</i> value ¹
Diuretic (thiazide and loop)	1131 (50.1)	1107 (49.1)	0.475
CCB (dihydropyridine)	905 (40.1)	930 (41.2)	0.449
CCB (non- dihydropyridine)	102 (4.5)	90 (4.0)	0.376
Beta blocker	783 (34.7)	767 (34.0)	0.616
Alpha blocker	544 (24.1)	558 (24.7)	0.628
Central agent	111 (4.9)	117 (5.2)	0.683
Vasodilator	19 (0.8)	15 (0.7)	0.491
RAS blocker	1416 (62.8)	1383 (61.3)	0.311
Dual RAS blockers	145 (6.4)	163 (7.2)	0.288
Spironolactone/eplerenone	84 (3.7)	73 (3.2)	0.372

¹Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.

CCB: Calcium channel blocker, RAS: Renin angiotensin system.

Table 7 Number of patients prescribed with each antihypertensive class at baseline and the 12-mo and 24-mo follow-ups

Antihypertensive class	Baseline, <i>n</i> = 1708 ¹	12-mo follow-up, <i>n</i> = 1708 ¹	24-mo follow-up, <i>n</i> = 1708 ¹	<i>P</i> value ¹
Diuretic (thiazide and loop)	895 (52.4)	874 (51.2)	839 (49.1)	0.153
CCB (dihydropyridine)	696 (40.7)	710 (41.6)	646 (37.8)	0.063
CCB (non- dihydropyridine)	83 (4.9)	74 (4.3)	75 (4.4)	0.719
Beta blocker	588 (34.4)	581 (34.0)	560 (32.8)	0.573
Alpha blocker	421 (24.6)	433 (25.4)	394 (23.1)	0.281
Central agent	81 (4.7)	90 (5.3)	66 (5.0)	0.779
Vasodilator	18 (1.1)	14 (0.8)	18 (1.1)	0.724
RAS blocker	1076 (63.0)	1077 (63.1)	1056 (61.8)	0.417
Dual RAS blockers	99 (5.8)	127 (7.4)	122 (7.1)	0.127
Spironolactone/eplerenone	58 (3.4)	49 (2.9)	43 (2.5)	0.309

¹Absolute number for frequencies (percentages). The *P* values were calculated by the χ^2 test.

CCB: Calcium channel blocker, RAS: Renin angiotensin system.

Table 8 Patient proportion achieving blood pressure < 140/90 mmHg at the 12-mo and 24-mo follow-ups in comparison to baseline

Time	Total number of patients	Number of patients with BP < 140/90 mmHg ¹	<i>P</i> value ¹
Baseline	3230	1549 (48.0)	-
12-mo follow-up	2096	1083 (52.0)	0.008
24-mo follow-up	1541	797 (51.7)	0.015

¹Absolute number for frequency (percentage). The *P* values were calculated by the χ^2 test.

BP: Blood pressure.

Linear regression analysis concluded that the annual rate of decline in eGFR was significantly higher in patients receiving three or more antihypertensive agents (-1.79 *vs* -1.07 mL/min/1.73 m²/year, *P* < 0.001) compared to those receiving less (Table 12).

Table 9 Patient proportion achieving blood pressure < 140/90 mmHg at the 12-mo and 24-mo follow-ups in comparison to baseline (patients on three or more antihypertensive agents)

	Total number of patients on three or more agents	Number of patients with BP < 140/90 mmHg ¹	P value ¹
Baseline	1383	629 (45.5)	-
12-mo follow-up	961	473 (49.2)	0.074
24-mo follow-up	724	359 (49.6)	0.072

¹Absolute number for frequency (percentage). The *P* values were calculated by the χ^2 test.

BP: Blood pressure.

Table 10 Cox regression analysis demonstrating associations between the prescription of three or more antihypertensive agents with all-cause mortality

Analysis	HR (95%CI) ¹	P value ¹
Univariate model	1.55 (1.41-1.69)	< 0.001
Multivariate model 1 ²	1.33 (1.21-1.45)	< 0.001
Multivariate model 2 ³	1.23 (1.12-1.35)	< 0.001
Multivariate model 3 ⁴	1.15 (1.04-1.27)	0.006

¹Absolute number for hazard ratio alongside corresponding 95% confidence interval and *P* value.

²Multivariate model 1: adjusted for age, sex, ethnicity, smoking status, and alcohol intake.

³Multivariate model 2: adjusted for all covariates of model 1 plus diabetes, any cardiovascular disease (ischemic heart disease or myocardial infarction or congestive cardiac failure or cerebrovascular accident or peripheral vascular disease), and blood pressure control < 140/90 mmHg.

⁴Multivariate model 3: adjusted for all covariates of model 2 plus estimated glomerular filtration rate and urine albumin-creatinine ratio.

HR: Hazard ratio; 95%CI: 95% confidence interval.

Table 11 Cox regression analysis demonstrated associations between the prescription of three or more antihypertensive agents with progression to end stage kidney disease

Analysis	HR (95%CI) ¹	P value ¹
Univariate model	1.60 (1.39-1.84)	< 0.001
Multivariate model 1 ²	1.81 (1.56-2.10)	< 0.001
Multivariate model 2 ³	1.55 (1.37-1.76)	< 0.001
Multivariate model 3 ⁴	1.31 (1.14-1.50)	< 0.001

¹Absolute number for hazard ratio alongside corresponding 95% confidence interval and *P* value.

²Multivariate model 1: adjusted for age, sex, ethnicity, smoking status, and alcohol intake.

³Multivariate model 2: adjusted for all covariates of model 1 plus diabetes, any cardiovascular disease (ischemic heart disease or myocardial infarction or congestive cardiac failure or cerebrovascular accident or peripheral vascular disease), and blood pressure control < 140/90 mmHg.

⁴Multivariate model 3: adjusted for all covariates of model 2 plus estimated glomerular filtration rate and urine albumin-creatinine ratio.

HR: Hazard ratio; 95%CI: 95% confidence interval.

DISCUSSION

In this study, we evaluated antihypertensive prescription patterns in patients from the SKS-CKD database, corresponding this to baseline eGFR, uACR, primary kidney disease aetiology and the presence of cardiovascular morbidities, and monitored prescription patterns over a 24-mo follow-up period. The number of antihypertensive agents prescribed for each patient was correlated with clinical outcomes, namely all-cause mortality and progression to ESKD.

Across the SKS-CKD cohort at baseline, RAS blockers were the most commonly prescribed agents for management of hypertension, followed by diuretics, dihydropyridine CCBs, and beta blockers. RAS blocker prescriptions decreased in patients with CKD stage 5 at baseline, whereas diuretics, dihydropyridine CCBs, and beta blockers were prescribed more frequently for patients with lower eGFR. Surprisingly, although it has not been widely advocated for use as an antihypertensive in current guidelines, alpha blockers were amongst the more commonly prescribed antihypertensive agents

Table 12 Rate of decline in estimated glomerular filtration rate in patients with three or more antihypertensive agents vs less than three antihypertensive agents prescribed

eGFR	Three or more agents prescribed ¹	Less than three agents prescribed ¹	P value ¹
² Delta eGFR, mL/min/1.73 m ² /yr	-1.79 (-4.25 to -0.07)	-1.07 (-3.10 to 0.72)	< 0.001

¹Expressed as a median (interquartile range). The P value was calculated by the Mann-Whitney U test.
²Delta estimated glomerular filtration rate analysis included 3068 patients with estimated glomerular filtration rate data available as defined.
eGFR: Estimated glomerular filtration rate.

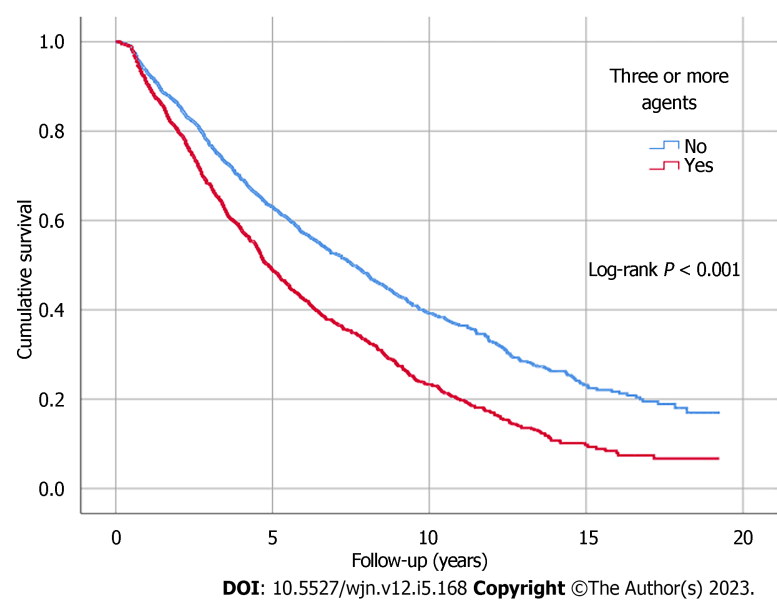


Figure 1 Kaplan-Meier analysis demonstrated associations between the prescription of three or more antihypertensive agents and all-cause mortality (log-rank, $P < 0.001$).

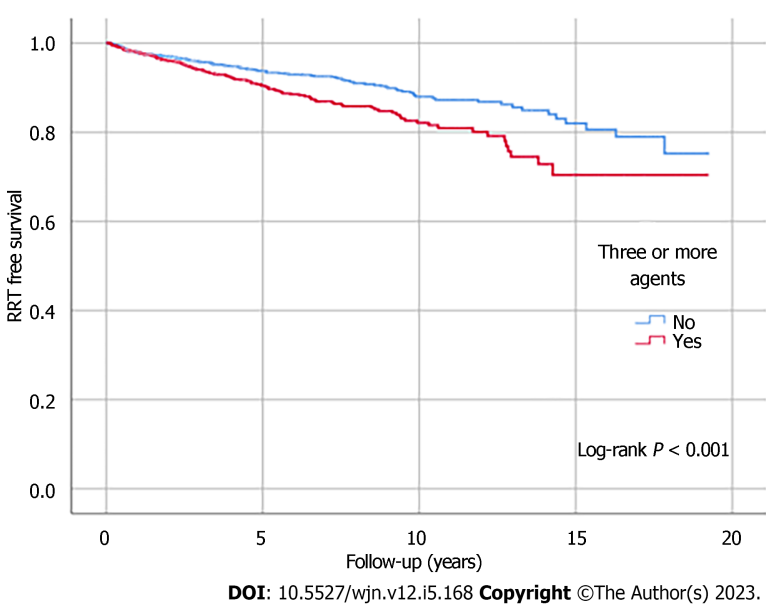


Figure 2 Kaplan-Meier analysis demonstrated associations between the prescription of three or more antihypertensive agents and renal replacement therapy free survival (log-rank, $P < 0.001$). RRT: Renal replacement therapy.

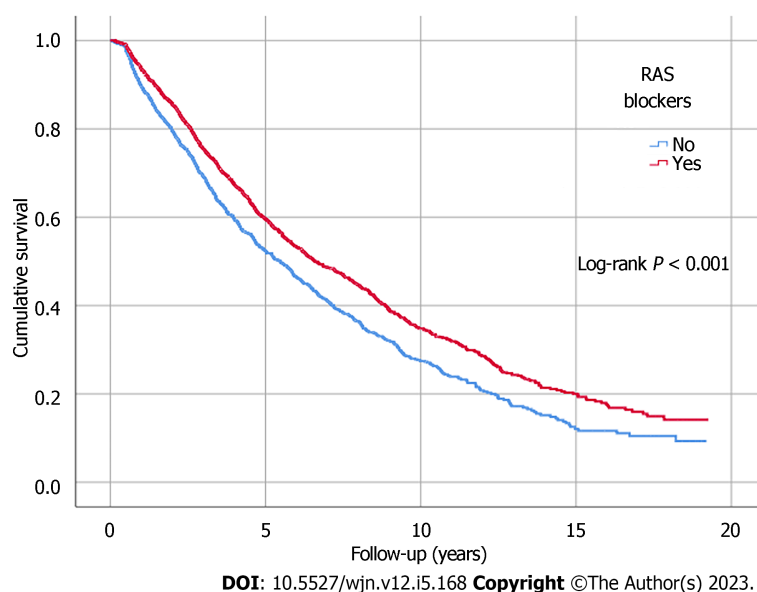


Figure 3 Kaplan-Meier analysis demonstrated associations between being prescribed renin angiotensin system blocker at baseline and all-cause mortality (log-rank, $P < 0.001$). RAS: Renin angiotensin system.

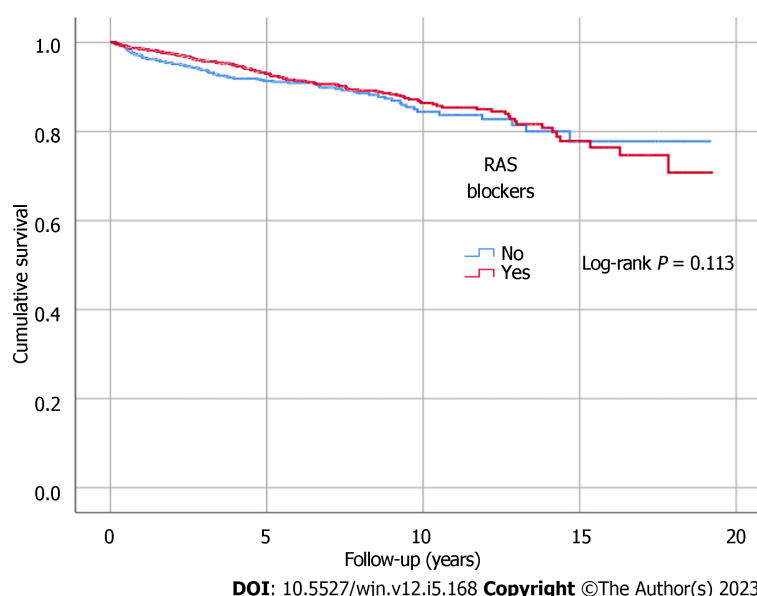


Figure 4 Kaplan-Meier analysis demonstrated associations between being prescribed renin angiotensin system blocker at baseline and renal replacement therapy free survival (log-rank, $P = 0.136$). RAS: Renin angiotensin system.

amongst patients in SKS-CKD, especially for those in the lower eGFR ranges. A major adverse effect of alpha blockers is orthostatic hypotension in patients with kidney function impairment[20-22]. The purposes of prescribing alpha blockers may not be solely for lowering of BP, as a substantial proportion of patients with benign prostatic hyperplasia are routinely initiated on them to relieve symptoms and improve urinary flow[23].

RAS blockers, diuretics, and dihydropyridine CCBs were prescribed with increasing frequency in patients with a greater degree of uACR. Ultimately, with an increase in the uACR category, a greater proportion of patients were prescribed more antihypertensive agents. RAS blockers remain the primary antihypertensive agents prescribed for patients with all forms of primary kidney disease. For CKD patients with CCF, the prescriptions of diuretics, beta blockers, and potassium sparing diuretics (spironolactone and eplerenone) were significantly higher compared to those without. This pattern was similar when comparing antihypertensive prescribing patterns between CKD patients with pre-existing cardiovascular events and those without.

Our analysis demonstrated that antihypertensive prescribing patterns at 12 mo and 24 mo had only minimally changed compared to baseline, but this was most likely because most patients had been enrolled in the renal service well before entry into the SKS. When determining associations between the number of antihypertensive agents prescribed and clinical outcomes, patients receiving a higher number of antihypertensive agents had worsened outcomes, namely

increased all-cause mortality and reaching ESKD. Such associations remained following adjustment of baseline demographic factors (*i.e.* age, sex, ethnicity, smoking status, and alcohol intake), plus diabetes, cardiovascular comorbidities, baseline eGFR, and uACR.

Consensus recommendation to commence ACEI or angiotensin receptor ARB as a first-line antihypertensive treatment option for CKD patients, particularly for those with proteinuria and/or reduced eGFR defined by $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ has been reached across the major international societies in cardiology and nephrology such as the American College of Cardiology, the American Heart Association, and KDIGO[8,24]. The updated 2021 KDIGO clinical practice guideline for BP management in CKD continues to advocate this approach in patients with hypertension and CKD, with or without diabetes, and not receiving dialysis[24]. Where an adult patient has a transplanted kidney, commencing an ARB or dihydropyridine CCB has been recommended[24]. In the United Kingdom, the National Institute of Health and Care Excellence (NICE) guideline defines BP targets (clinic measured) for patients with CKD according to the patient's uACR[25]. Adult CKD patients are divided into 2 groups: those with a uACR $< 70 \text{ mg/mmol}$ (618.8 mg/g); and those with a uACR $> 70 \text{ mg/mmol}$ (618.8 mg/g). In patients with a uACR $< 70 \text{ mg/mmol}$ (618.8 mg/g), the BP target is below 140/90 mmHg, whereas in patients with a uACR $> 70 \text{ mg/mmol}$ (618.8 mg/g), the BP target is below 130/80 mmHg.

An ACEI or ARB is first-line treatment for hypertension in CKD patients with uACR $> 30 \text{ mg/mmol}$ (265.2 mg/g). A thiazide diuretic or CCB is to be used as second-line medications. While both dihydropyridine CCB and non-dihydropyridine CCB have been shown to have similar effects in terms of BP control, non-dihydropyridine CCBs such as verapamil and diltiazem have been shown to reduce proteinuria to a greater extent. However, prescribing non-dihydropyridine CCBs over dihydropyridine CCBs would generally appear to be less popular in actual clinical practice, mainly due to concerns of increased risk of cardiac adverse effects such as bradycardia that could be potentially life-threatening in severe cases[26]. A potassium sparing agent such as spironolactone can also be added, but due to the increased risk of hyperkalaemia, this is recommended only if there is persistent poor BP control following the addition of a thiazide diuretic. Whilst these are the main antihypertensive options as per NICE guidelines, other antihypertensive classes exist, such as alpha blockers, direct renin inhibitors, vasodilators, and centrally acting antihypertensive agents. These medications are not currently recommended under the NICE and other international guidelines for various reasons, such as the presence of adverse effects as well as the lack of evidence that they offer a strong clinical benefit for CKD patients with hypertension.

A number of studies have been conducted reviewing antihypertensive prescribing patterns in patients with CKD. Amongst the more recent studies that have followed the introduction of updated hypertension guidelines, a study conducted by Magvanjav *et al*[12] utilized electronic health record data from 5658 CKD patients with hypertension to examine their antihypertensive drug prescribing patterns, BP control, and risk factors for resistant hypertension. As found in our study and in observational data stated from recent hypertension guidelines, Magvanjav *et al*[12] noted that 64% of patients were prescribed an ACEI or ARB. They also concluded that BP was better controlled in patients who were prescribed a combination of medications that included a diuretic and beta blocker. Another study by Alencar de Pinho *et al*[13] compared antihypertensive prescribing patterns in CKD patients internationally and similarly found that ACEI or ARB was the most commonly prescribed antihypertensive class. However, the investigators noted significant variations in antihypertensive medication prescribing practices globally for all antihypertensive agents across different stages of CKD. Taking ACEI or ARB for example, Alencar de Pinho *et al*[13] observed that the prevalence of an ACEI or ARB prescription varied between 54% and 91% across different countries. This emphasizes that significant variations remain regarding clinicians' approaches to antihypertensive treatment prescription for their CKD patients within the real-world setting, whether they follow a guideline-recommended algorithm or basing their approach from personal clinical experiences and preferences.

Indeed there are numerous patient-specific and clinical challenges when treating hypertension in CKD, of which clinician variation in antihypertensive prescription practices is only one issue. This conundrum may be explained by the variability in national and international guideline recommendations at present. Areas where a global consensus has not been reached are the BP thresholds that determine when treatment initiation is indicated, for instance. There also remains no unified agreement on the BP targets to be achieved amongst CKD patients. More importantly, there is continuous debate and discussion on how best to optimize antihypertensive therapy for BP control and cardiorenal protection. These are avenues of research where further work is required.

There is now an increased indication for adding sodium glucose cotransport (SGLT2) inhibitors to the current portfolio of recommended medications for hypertension management in CKD, given their emergence as a therapeutic option for cardiorenal protection in people with and without diabetes[27]. Large, randomized, placebo-controlled trials have pointed to the potential of SGLT2 inhibitors as having positive effects on BP control in both office and out-of-office contexts. The SACRA, EMPA-REG BP, and CREDENCE trials were amongst the clinical trials that have made these conclusions[28-30]. The post hoc analysis of the CREDENCE trial demonstrated the BP-lowering effect of canagliflozin for patients with resistant hypertension, which is novel and encouraging[29]. Additional studies are needed to validate the role of SGLT2 inhibitors in optimizing BP control and reducing adverse cardiovascular outcomes amongst patients living with CKD and hypertension, particularly those with resistant hypertension.

Despite the main strength of our study being inclusion of an ethnically and socioeconomically diverse CKD patient group, as well as being conducted over a 20-year period, there are limitations to acknowledge. One limitation was an inability to clearly correlate details relating to the indication(s) for antihypertensive medication prescription and any adjustments during the follow-up period due to multiple clinicians being involved in a patient's management. Furthermore, it is unclear if diuretics were prescribed as an antihypertensive agent within this context, or intended for other clinical purposes (*e.g.*, for peripheral oedema). Understanding the indications for prescription of particular antihypertensive medication(s) would have been useful in determining the true patterns of antihypertensive prescribing practices in this study. Also, as our centre does not complete urinary antihypertensive screens routinely, there is always

the confounding impact of drug non-compliance amongst patients receiving three or more antihypertensive agents. This contributes to poor BP control and its associated morbidity and mortality outcomes. Finally, there was incomplete data on determining the rate of decline in eGFR when comparing between CKD patients with three or more antihypertensive agents *vs* less than three antihypertensive agents prescribed due to delta eGFR data being unavailable for 162 patients (5% of entire cohort).

CONCLUSION

In summary, RAS blockers were found to be the most commonly prescribed antihypertensive agents, followed by diuretics and CCBs, which are recommended as second-line antihypertensive treatment options. Diuretics, beta blockers, and mineralocorticoid antagonists were found to be more commonly prescribed in CKD patients with cardiovascular comorbidities. Whilst our study results aligned with that of expectations from the current NICE guideline algorithm, further work determining optimal strategies in approaching antihypertensive prescription for CKD patients at both an individual and policy level is needed to reduce the variations currently observed in clinical practice. The opportunity to introduce newer and potentially more cost-effective therapies in the form of SGLT2 inhibitors for hypertension management in CKD is attractive and could be revolutionary in addressing these challenges, and continued research in this area is anticipated.

ARTICLE HIGHLIGHTS

Research background

Hypertension is a major contributor towards the progression of chronic kidney disease (CKD) and a leading consequence of CKD. Despite standard guidelines, clinician practices on managing hypertension in CKD patients remain variable.

Research motivation

It is important to explore the factors relating to CKD patients that influences a clinician's decision to use specific antihypertensive agents with the aim to better standardize current antihypertensive prescription practices.

Research objectives

To investigate hypertension management practices in CKD patients within a real-world setting.

Research methods

We retrospectively analysed patients recruited into the Salford Kidney Study database. Data including patient demographic information, comorbidities, and a detailed antihypertensive medication history were reviewed. Prescription patterns of antihypertensive agents were explored based on estimated glomerular filtration rate expressed as mL/min/1.73 m², urine albumin-creatinine ratio, primary kidney disease aetiology, and cardiovascular disease. The association between being prescribed three or more antihypertensive agents and clinical outcomes (*i.e.* all-cause mortality and reaching end stage kidney disease) was also studied.

Research results

A total of 3230 non-dialysis dependent CKD patients with data collected between October 2002 and December 2019 were included. The most frequently prescribed antihypertensive agents were renin angiotensin system blockers (61%), followed by diuretics (47%), dihydropyridine calcium channel blockers (39%), and beta blockers (34%). A greater proportion of patients were taking three or more antihypertensive agents with advancing CKD stages (53% of CKD stage 5 patients *vs* 26% of CKD stage 2 patients) and as the urine albumin-creatinine ratio increased (category A3: 62% *vs* category A1: 40%, $P < 0.001$). The prescription of three or more antihypertensive agents was associated with all-cause mortality, independent of blood pressure control (hazard ratio: 1.15; 95% confidence interval: 1.04-1.27, $P = 0.006$).

Research conclusions

Renin angiotensin system blockers were found to be the most prescribed antihypertensive agents, followed by diuretics and calcium channel blockers. Outcomes were poorer in CKD patients with poor blood pressure control despite being on multiple antihypertensive agents.

Research perspectives

Our study results aligned with expectations from the current National Institute of Health and Care Excellence guideline algorithm; further work determining optimal strategies in approaching antihypertensive prescriptions for CKD patients at both an individual and policy level is needed to reduce the variations currently observed in clinical practice.

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FOOTNOTES

Author contributions: Chinnadurai R drafted the manuscript, led the design and oversight of the study, led the data analysis, and participated in drafting and revising the manuscript; Wu HHL drafted the manuscript and participated in revising the manuscript; Abuomar J participated in the design of the study and led data collection; Rengarajan S participated in the design of the study and assisted in data collection; New D participated in revising the manuscript; Green D participated in revising the manuscript; Kalra PA supervised the design and oversight of the study and participated in revising the manuscript; All authors read and approved the final manuscript.

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Heterogeneity in cardiorenal protection by Sodium glucose cotransporter 2 inhibitors in heart failure across the ejection fraction strata: Systematic review and meta-analysis

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Abstract

BACKGROUND

Gliflozins or Sodium glucose cotransporter 2 inhibitors (SGLT2i) are relatively novel antidiabetic medications that have recently been shown to represent favorable effects on patients' cardiorenal outcomes. However, there is shortage of data on potential disparities in this therapeutic effect across different patient subpopulations.

AIM

To investigate differential effects of SGLT2i on the cardiorenal outcomes of heart failure patients across left ventricular ejection fraction (LVEF) levels.

METHODS

Literature was searched systematically for the large randomized double-blind controlled trials with long enough follow up periods reporting cardiovascular and renal outcomes in their patients regarding heart failure status and LVEF levels. Data were then meta-analyzed after stratification of the pooled data across the LVEF strata and New York Heart Associations (NYHA) classifications for heart failure using Stata software version 17.0.

RESULTS

The literature search returned 13 Large clinical trials and 13 *post hoc* analysis reports. Meta-analysis of the effects of gliflozins on the primary composite outcome showed no significant difference in efficacy across the heart failure subtypes, but higher efficacy were detected in patient groups at lower NYHA classifications ($I^2 = 46\%$, $P = 0.02$). Meta-analyses across the LVEF strata revealed that a baseline LVEF lower than 30% was associated with enhanced improvement in the primary composite outcome compared to patients with higher LVEF levels at the borderline statistical significance (HR: 0.70, 95%CI: 0.60 to 0.79 *vs* 0.81, 95%CI: 0.75 to 0.87; respectively, $P = 0.06$). Composite renal

outcome was improved significantly higher in patients with no heart failure than in heart failure patients with preserved ejection fraction (HFpEF) (HR: 0.60, 95%CI: 0.49 to 0.72 *vs* 0.94, 95%CI: 0.74 to 1.13; $P = 0.04$). Acute renal injury occurred significantly less frequently in heart failure patients with reduced ejection fraction who received gliflozins than in HFpEF (HR: 0.67, 95%CI: 0.51 to 0.82 *vs* 0.94, 95%CI: 0.82 to 1.06; $P = 0.01$). Volume depletion was consistently increased in response to SGLT2i in all the subgroups.

CONCLUSION

Heart failure patients with lower LVEF and lower NYHA sub-classifications were found to be generally more likely to benefit from therapy with gliflozins. Further research are required to identify patient subgroups representing the highest benefits or adverse events in response to SGLT2i.

Key Words: Sodium glucose cotransporter 2 inhibitors; Cardiovascular; Renal outcome; efficacy; Heart failure with preserved ejection fraction; Heart failure with reduced ejection fraction

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Core Tip: Compared to placebo, treatment with Sodium glucose cotransporter 2 inhibitors improve cardiorenal outcomes in a broad range of disorders with significant heterogeneity in the subgroup of patients who are likely to benefit most from the treatment across their heart failure subtypes, New York Heart Associations classifications and ejection fraction levels. There are also adverse events associated with these drugs that deserve further research.

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INTRODUCTION

Anti-hyperglycemic medications have been shown to improve cardiovascular outcomes and renal health in a range of disorders; yet in specific patient subpopulations there is a possibility that their side effects outweigh the protection they offer. For the same reason, large and expensive clinical trials have been conducted to investigate their impact on health entities, and protective roles have been reported for a number of these drugs that went beyond their antihyperglycemic effects[1,2].

Gliflozins or Sodium glucose cotransporter 2 inhibitors (SGLT2i) are relatively novel antidiabetic medications that lower blood levels of glucose through increasing its urinary excretion and therefore they also induce weight loss[1]. Recently a number of large clinical trials have shown significant cardiorenal protection by these drugs in a spectrum of diseases including patients with type 2 diabetes mellitus (T2DM), heart failure and chronic kidney diseases. However, the patient populations were inconsistent in these trials in several aspects, and there is a need for further research regarding the potential factors that might contribute in this effect. In fact, a number of systematic reviews have already been published covering a broad spectrum of cardiac, renal and metabolic factors, including meta-analyses showing significant improvements in the composite outcomes of cardiovascular death or hospitalizations in heart failure patients with either preserved (HFpEF) or reduced ejection fraction (HFrEF)[3-6]. The purpose of this systematic review and meta-analysis is to examine potential effects of SGLT2i therapy on the composite or specific cardiac or renal outcomes in heart failure patients across baseline left ventricular ejection fraction (LVEF) levels.

MATERIALS AND METHODS

Search strategy and selection criteria

Supplementary Figure 1 summarizes the search strategy of the current systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was followed in this study (Supplementary Figure 2). A systematic search of the literature was performed using Cochrane Library, Reference Citation Analysis, nejm.org, and EuropePMC search engines to April 15, 2023. Pubmed/MEDLINE could not be reached due to internet filtering. Further search of the literature was performed using Google Scholar to find the *post hoc* analyses and substudies from the included large randomized controlled trials, regarding the subjects of interest for this systematic review (Figure 1).

In order to minimize potential publication biases, the inclusion criteria assigned eligibility only to the reports of double-blind and placebo-controlled trials if they were large (defined as at least 1000 subjects in the SGLT2i arm and at least half as many patients in the placebo arm) with long enough follow up time (at least 6 mo), assessing SGLT2i, and reported any of the efficacy or safety outcomes of interest in this review, as specified. Finally 27 studies (13 trials and 14

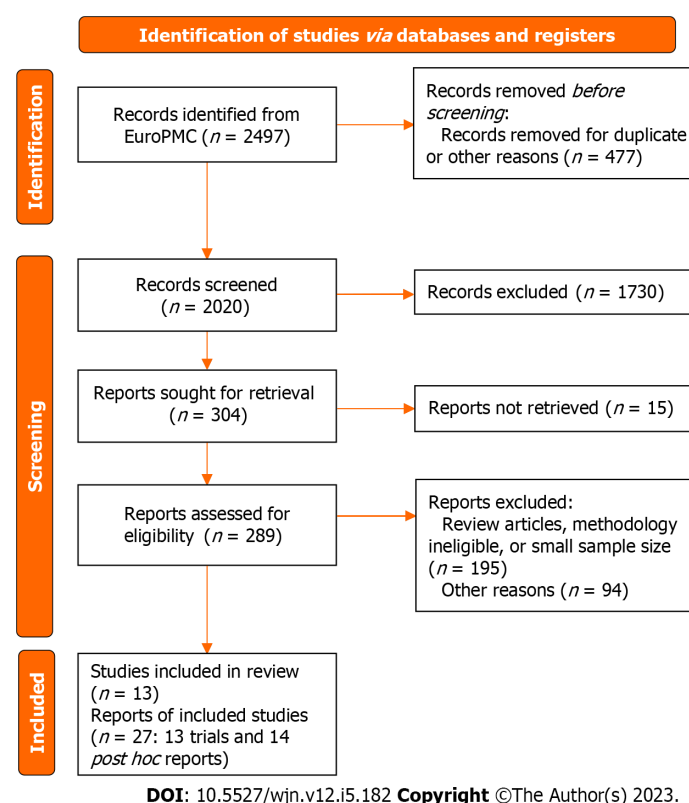


Figure 1 PRISMA flow diagram.

post hoc analyses) were found and reviewed[7-33].

Outcomes of interest

The evaluated outcomes in this systematic review and meta-analysis included the primary composite outcome as defined by each study and irrespective of the disparities between them, cardiovascular death, the composite outcome of cardiovascular death or hospitalization (or an urgent visit) for heart failure, composite renal outcome (serious renal events defined by different studies and irrespective of potential differences between trials) and death from any cause.

Specific renal outcomes: As mentioned above, the composite renal outcomes were inconsistently defined by different studies and included a heterogeneous combinations of the following indicators: Doubling of serum creatinine measures, substantial decrease in estimated glomerular filtration rate (*i.e.* $\geq 40\%$ decrease; falling below 60 to less than 15 mL/min/1.73 m² in different studies), end-stage kidney disease; renal replacement therapy initiation (*i.e.* dialysis or renal transplantation), and renal death. Wherever there were reports from more than one combination of renal outcomes, the one with the larger spectrum was used as the composite renal outcome for inclusion into the meta-analysis. Other renal outcomes that were evaluated in this study included renal disease progression/worsening renal function, acute kidney injury/acute renal failure, volume depletion, and diabetic ketoacidosis.

Stratifications across LVEF stratus

Heart failure subtypes: Data for primary outcomes of interests were extracted and meta-analysis were conducted across specific stratification strategies. The patients' heart failure status and the type of heart failure (*i.e.* HFpEF), HFrEF and mid-range/mildly-reduced ejection fraction (HFmrEF) were also extracted. The definition of HFpEF has varied across different trials, with HFpEF defined as EF $> 40\%$ in the EMPEROR-Preserved[16] and DELIVER[18], and as EF $\geq 50\%$ in the SCORED[13], CANVAS[12], EMPA-REG OUTCOME[21], and SOLOIST-WHF[17] trials. Likewise, HFrEF was inconsistently defined as EF $< 40\%$ in the SCORED[13] and SOLOIST-WHF[17], as $\leq 40\%$ in the EMPEROR-Reduced[15] and DAPA-HF[14], as EF $< 45\%$ in DECLARE-TIMI 58[33], as EF $\leq 45\%$ in the VERTIS-CV[24], and as EF $< 50\%$ in the CANVAS[22] and EMPA-REG OUTCOME[21] trials. Heart failure with mildly reduced (mid-range) EF was consistently defined as EF between 40%-49%. Only in Supplementary Figure 3, LVEF rates between 35% and 55% were also considered HFmrEF. Finally, heart failure not-otherwise-specified (nos) as patients diagnosed with heart failure (presence of signs and symptoms of HF, elevated levels of natriuretic peptides in the plasma and evidence of structural heart disease - left ventricular hypertrophy or left atrial remodeling - or the presence of diastolic dysfunction) with no further stratifications. Patients who had baseline LVEF ranged within the definitions but without the documented diagnosis of heart failure were excluded from the respective subgroups.

LVEF stratus: Meta-analyses of the outcomes were repeated after stratification of the LVEF rates by LVEF stratus (*i.e.* documented heart failure patients with LVEF measures above or below the cutoff values of 30%, 40%, 45%, 50%, and

60%). However, since the outcome analyses across all the predefined LVEF cutoff points were not exactly performed by all the reviewed studies, an alternative approach was employed wherever there were reports that fell in ranges totally within the study subgroups defined across the cutoff points of this study; *e.g.* in meta-analysis of outcomes across LVEF of 40%, if a trial had only provided data of LVEF over 50% or below 30%, the data were included as LVEF over 40% or $\leq 40\%$, respectively (since LVEF values $\geq 50\%$ falls totally within the range of $> 40\%$ and LVEF $< 30\%$ falls fully within the range of $\leq 40\%$). But data of patients with LVEF $< 50\%$ was not included into meta-analysis of patients with LVEF $< 40\%$, since it doesn't totally fall within the specified range. Moreover, if data was available for two LVEF ranges for any particular study, both falling within the meta-analysis ranges, the one that was closest to the cutoff and therefore encompassed the largest possible patient population was chosen for inclusion (*e.g.* if LVEF $> 45\%$ and $> 50\%$ were available for a trial, in meta-analysis of outcomes across LVEF 40%, data of LVEF $> 45\%$ was included in the reports of LVEF $> 40\%$).

Statistical analysis

Hazard ratio (HR) and 95% confidence interval (CI) were pooled using a random-effects DerSimonian and Laird model. Inverse of the variance was used to assign weights to each study. Heterogeneity among studies was assessed using the Higgins I^2 value. Meta-regression analysis was conducted using mixed-effects modelling to evaluate factors potentially explaining any observed heterogeneity for the study outcomes (*i.e.* composite study outcome, cardiovascular death and/or heart failure hospitalizations and composite or specific renal outcomes). Meta-regression models using demographic or disease-specific baseline data (*i.e.* age, gender, ethnicity, glycated hemoglobin, past medical history, *etc.*) inputs were not possible due the lack of the baseline data discriminately reported across the study groups (*i.e.* heart failure subtypes, LVEF cutoff levels and NYHA). The only factor that could be included into meta-regression without controversy was the type of gliflozins employed. Some other factors were also used for this purpose (including mean study follow-up time, T2DM and chronic kidney disease (CKD) as inclusion criteria to the study) which might sound controversial since the follow up times could be inconsistent in patient subgroups, as were T2DM and CKD status in studies not having them as inclusion criteria. Even though, no observed heterogeneity in any of the meta-analyses could be explained by the gliflozin type, with no significant effect returned by meta-regression analysis. The same observation was made for meta-regression analysis of the more controversial factors mentioned above.

No special dosage preferences were made for trials in which more than one SGLT2i dosage had been sought and the pooled effects were used for analyses wherever applicable and otherwise, data from the higher SGLT2i dosage was considered. Subgroup analysis was conducted to assess for variability of therapeutic effects across the LVEF strata, heart failure subtypes and NYHA subclass populations. Study quality was assessed using version 2 of the Cochrane risk-of-bias tool. 2-tailed P values with statistical significance specified at 0.05 were used in all analyses. Stata version 17 (Stata Corp.) and Microsoft Excel 2013 (Microsoft Corp.) were used for analyses.

RESULTS

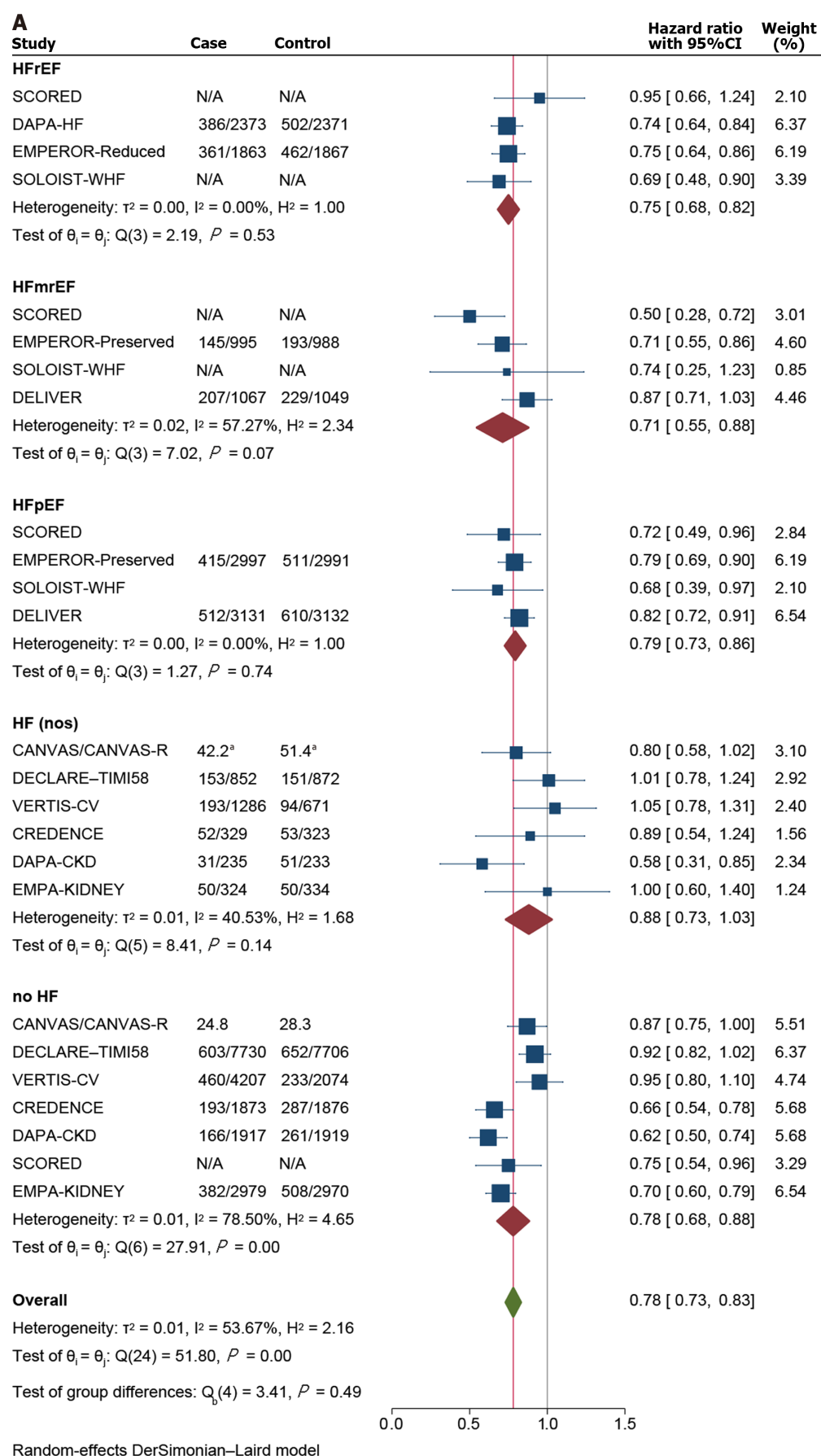
The literature search returned 13 large clinical trials evaluating impact of SGLT2i on the outcome of patients[7-19], and their characteristics are summarized in Table 1. Fourteen more studies reporting *post hoc* analysis of the reviewed trials were also found and reviewed[20-33]. Five trials were on heart failure patients, in seven trials only diabetic patients included and four trials were conducted specifically on patients with chronic kidney diseases. Patients' data and outcome reports were extracted regarding their heart failure status and included in the meta-analyses.

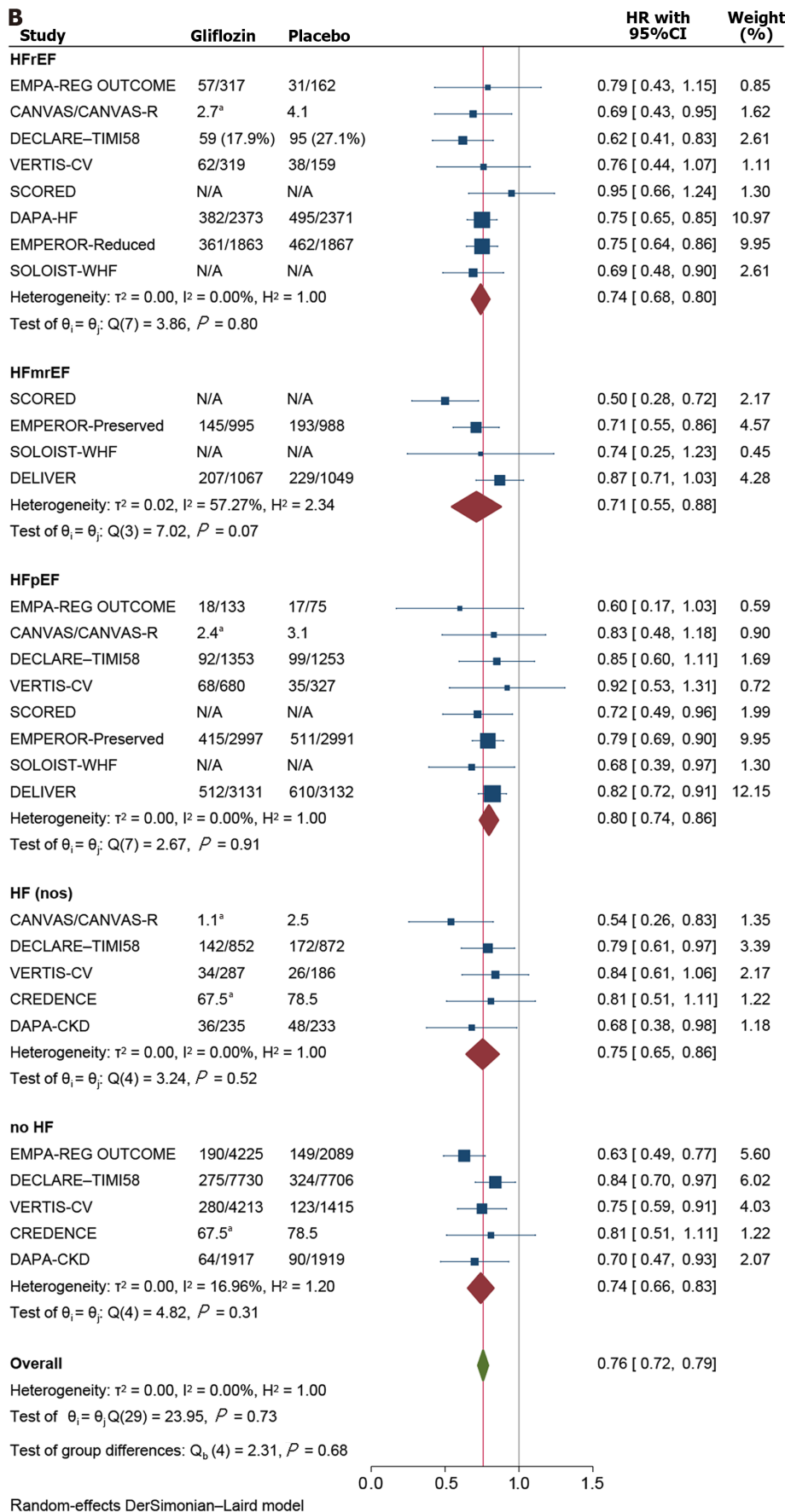
Meta-analyses across heart failure subtypes

Meta-analysis of the effects of gliflozins on the primary composite outcomes (cardiorenal events as defined by each study) showed that compared to placebo, SGLT2i significantly decreased the event rates (HR: 0.78, 95%CI: 0.73 to 0.83, $I^2 = 53.7\%$), with no significant difference in efficacy across the heart failure status or subtypes ($P = 0.49$, Figure 2A). Likewise, when cardiovascular death and/or urgent visits/hospitalization for heart failure was used as the outcome, gliflozins were superior to placebo with no heterogeneity between the subgroups (HR: 0.76, 95%CI: 0.72 to 0.79, $P = 0.68$, $I^2 = 0\%$, Figure 2B). Compared to placebo, SGLT2i therapy was again found to be significantly associated with lower cardiovascular death (HR: 0.84, 95%CI: 0.78 to 0.90, $I^2 = 19.9\%$) and all-cause mortality (HR: 0.86, 95%CI: 0.81 to 0.91, $I^2 = 32.1\%$), with no significant difference between the subgroups [$P = 0.98$ (Supplementary Figure 3) and $P = 0.21$ (Figure 3), respectively]. However, a trend toward higher effectiveness was observed for patients with HFrEF vs HFpEF; though it failed to reach the statistical significance just at the borderline level; $P = 0.07$ (Supplementary Figure 4).

Although no significant difference was detected in efficacy measures between the heart failure subtypes in any of the above-mentioned meta-analyses, interestingly SGLT2i seem to offer significant benefits in survival outcome (*i.e.* cardiovascular death or all-cause mortality) only to HFrEF or (to a lesser degree) HFmrEF patients, and the respective outcome effects did not reach significance level for HFpEF (HR: 0.89, 95%CI: 0.75 to 1.02; HR: 0.96, 95%CI: 0.88 to 1.05; respectively, Supplementary Figure 3 and Figure 3).

Meta-analyses of the primary composite outcomes across NYHA classes revealed significant improvement in the outcome rates [HR: 0.74(0.67-0.82)], although as is illustrated in Figure 4, this favorable effect was not consistent across all the NYHA subclasses and those at lower classes significantly better responded to SGLT2i ($I^2 = 46\%$, $P = 0.02$; Figure 4).

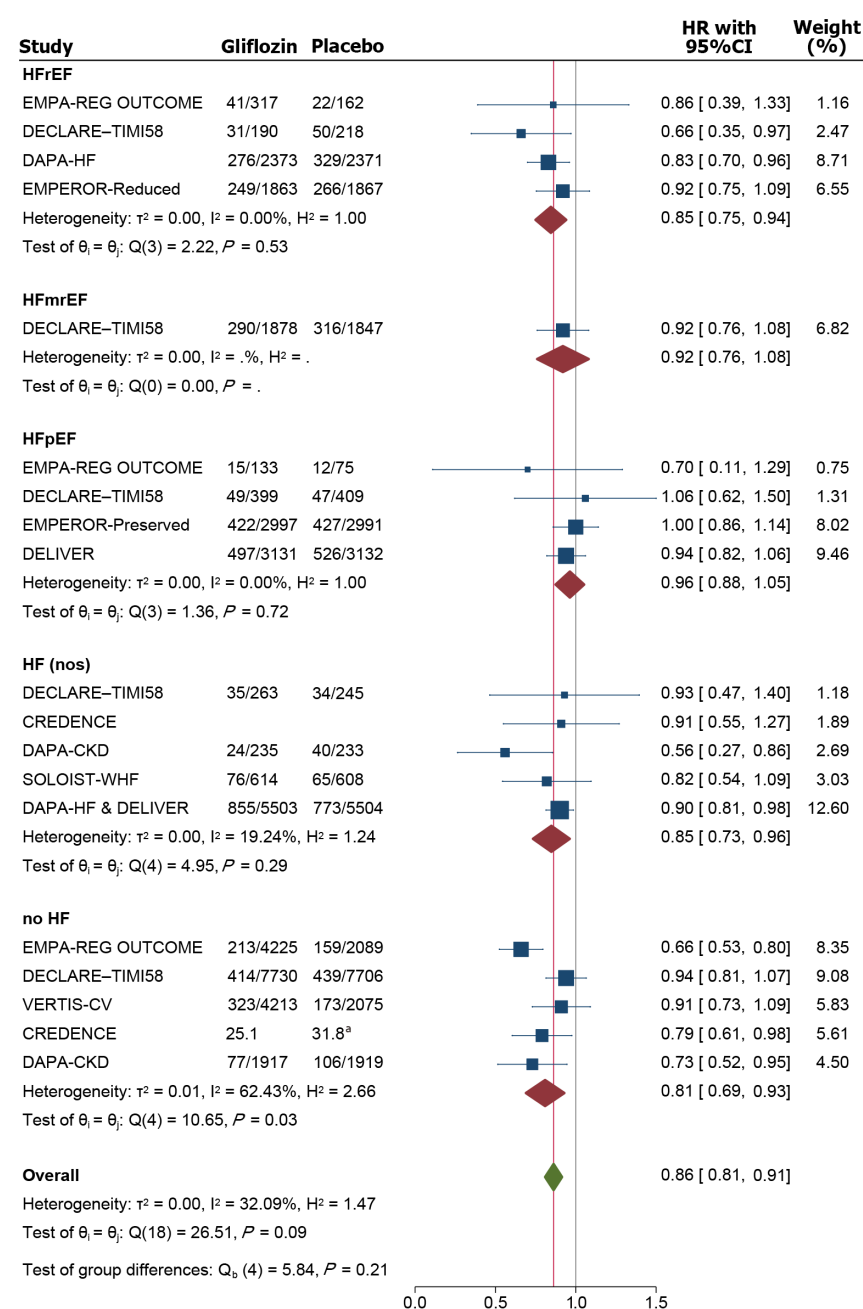




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Figure 2 Meta-analysis of primary composite outcome. A: Gliflozins' effect on the primary composite outcome across heart failure subtypes; B: Gliflozins' effect on the composite outcome of 'cardiovascular deaths or hospitalizations due to heart failure or urgent visits' across heart failure subtypes. HF: Heart failure;

HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified; N/A: Not available. ^aper 1000 person-years; ^bper 100 person-years.



Random-effects DerSimonian-Laird model

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Figure 3 Meta-analysis of the effects of Sodium glucose cotransporter 2 inhibitors on the all-cause mortality across the heart failure subtypes. HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified. ^aper 1000 person-years.

Meta-analysis across LVEF stratum

Meta-analyses were repeated across the LVEF stratum, irrespective of the authors' definitions of the heart failure subtypes. The primary composite outcomes across all the LVEF cutoff levels showed significant efficacy for gliflozins compared to placebo, with no significant difference between the subgroups. Notably, patients with a baseline LVEF of 30% or less represented enhanced improvement in the primary composite outcome compared to patients with LVEF over 30%, but at the borderline statistical significance (HR: 0.70, 95%CI: 0.60 to 0.79 *vs* 0.81, 95%CI: 0.75 to 0.87; respectively, $P = 0.06$; [Supplementary Figure 4](#)).

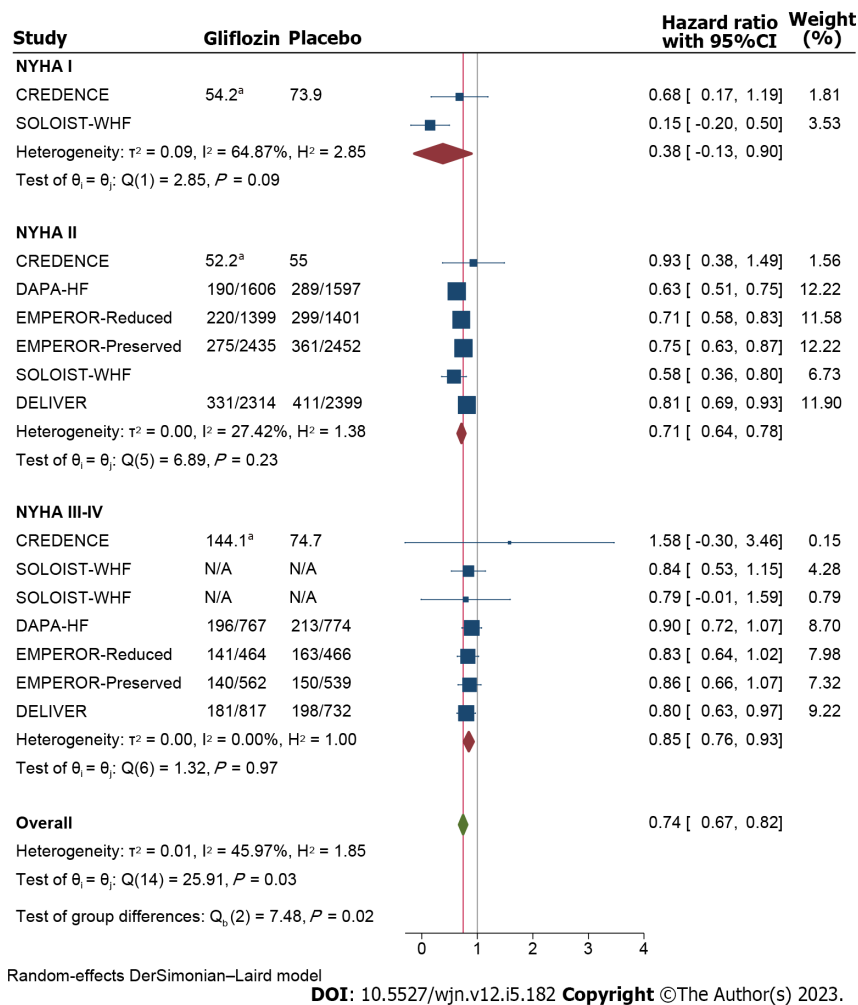


Figure 4 Meta-analysis of the effects of Sodium glucose cotransporter 2 inhibitors on the primary composite outcome of heart failure patients across different New York Heart Associations classifications. ^aper 1000 person-years.

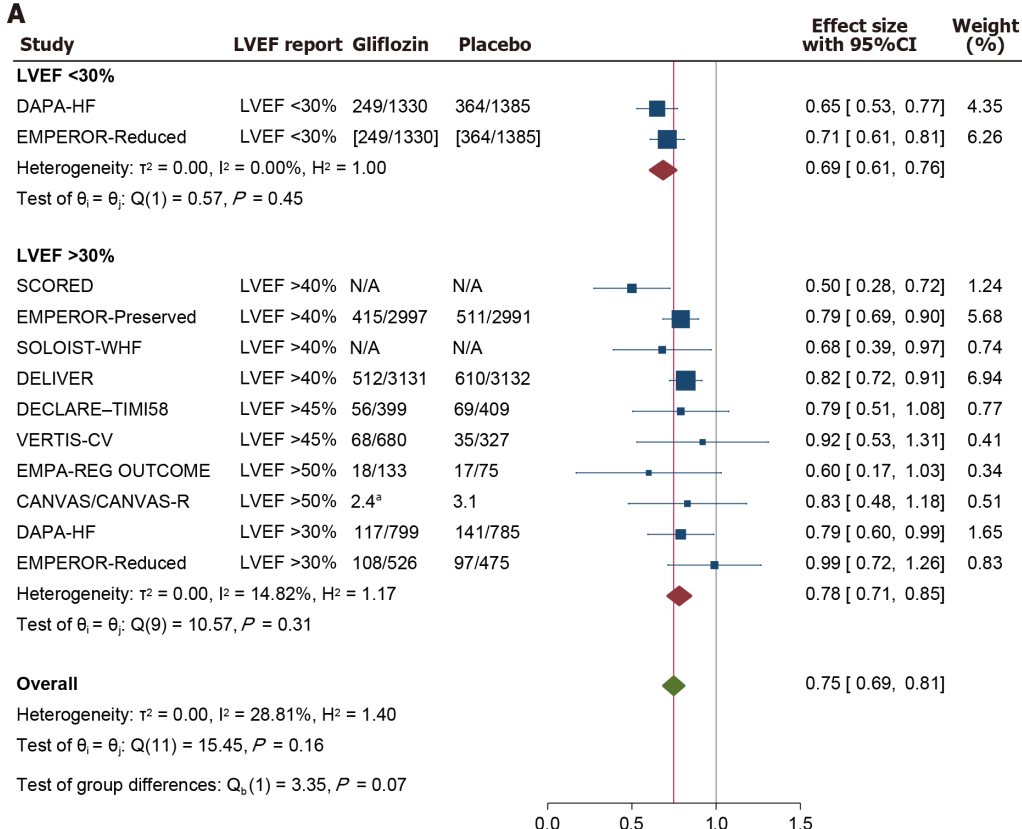
Similar to the results of primary outcome analyses, meta-analysis of the composite outcome of ‘cardiovascular death or hospitalizations (or urgent visits) due to heart failure’ exhibited significant improvement in response to treatment with SGLT2i at all the LVEF levels though again, compared to patients with LVEF above 30%, the subgroup of patients with the baseline LVEF of 30% or less showed a stronger response to gliflozins at borderline significance (HR: 0.69, 95%CI: 0.61 to 0.76 *vs* 0.78, 95%CI: 0.71 to 0.85; $P = 0.07$). Further analyzes at higher cutoff values showed no significant difference for the respective outcome ($P > 0.4$ for all; **Figure 5**). All-cause mortality also showed significant benefit across LVEF strata with the relatively best effect size in patients with LVEF $\leq 40\%$ (versus LVEF $> 40\%$) but no statistical significance was reached; **Figure 6**.

Renal outcome meta-analyses across heart failure subtypes

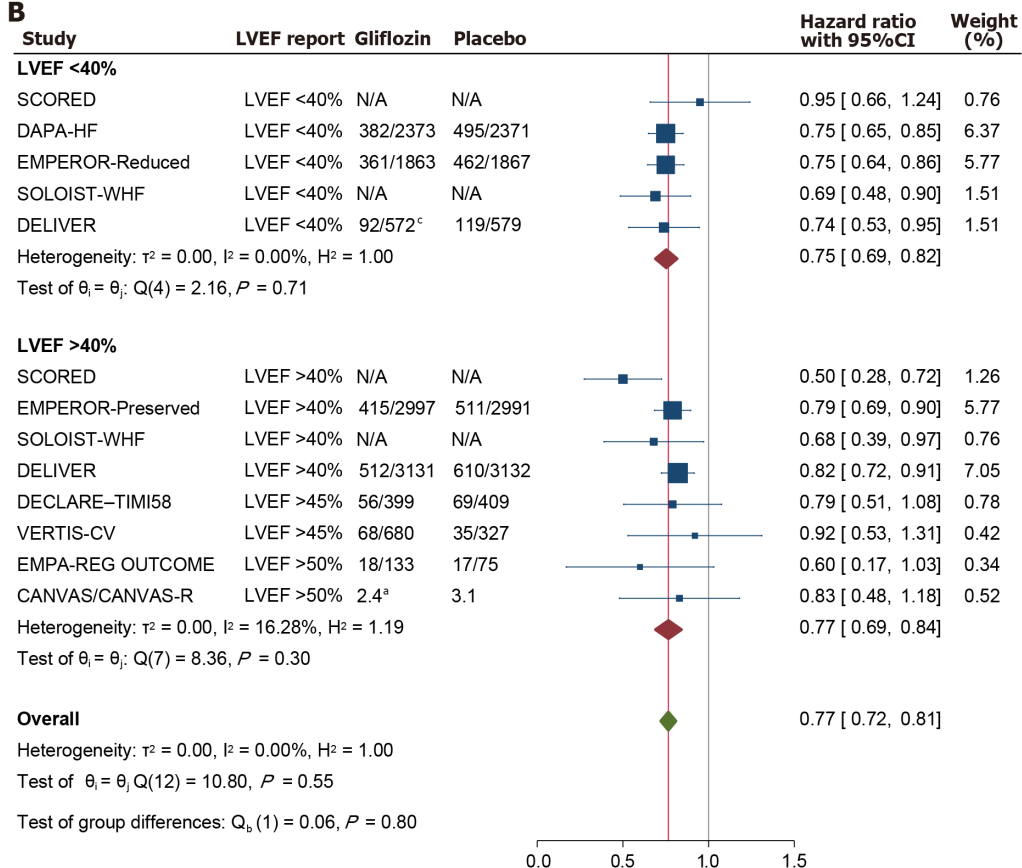
Composite renal events: Composite renal events was an unspecific terminology that comprised a diverse spectrum of unfavorable renal events (described in methods) As could be perceived from **Figure 6A**, SGLT2i significantly improved composite renal events as compared to the placebo-treated group (HR: 0.69, 95%CI: 0.59 to 0.79), but significant difference across the meta-analysis patient groups was observed with HFpEF and no-heart failure patients representing the lowest and the highest response rates, respectively (HR: 0.94, 95%CI: 0.74 to 1.13 and 0.60, 95%CI: 0.49 to 0.72, respectively); $P = 0.04$, **Figure 7**.

Acute kidney injury (or acute renal failure) was also shown to occur significantly less frequently in patients receiving SGLT2i compared to placebo (HR: 0.83, 95%CI: 0.75 to 0.92; **Figure 7B**); however this effect was not consistent across the heart failure groups and HFpEF and HFpEF patients respectively represented the highest and the lowest response rates with significant difference between, after excluding other subgroups from the meta-analysis (HR: 0.67, 95%CI: 0.51 to 0.82 *vs* 0.94, 95%CI: 0.82 to 1.06; $P = 0.01$, **Supplementary Figure 5**).

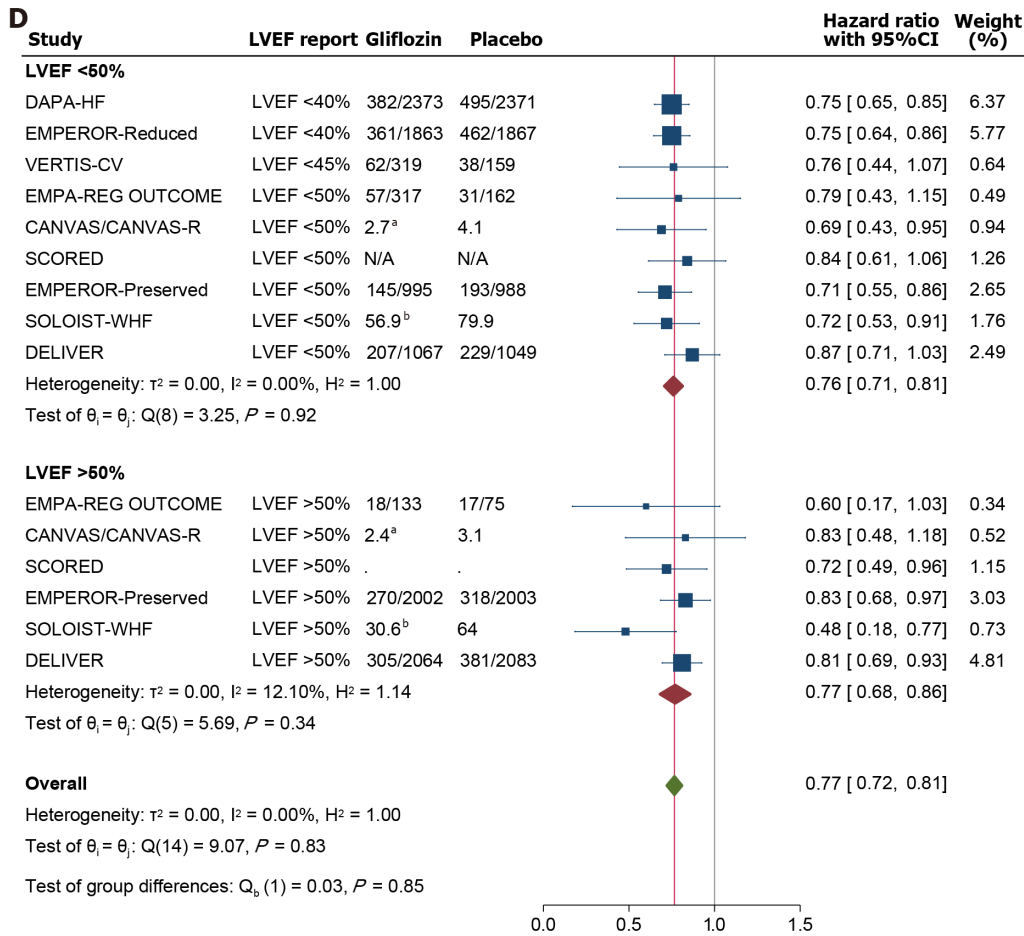
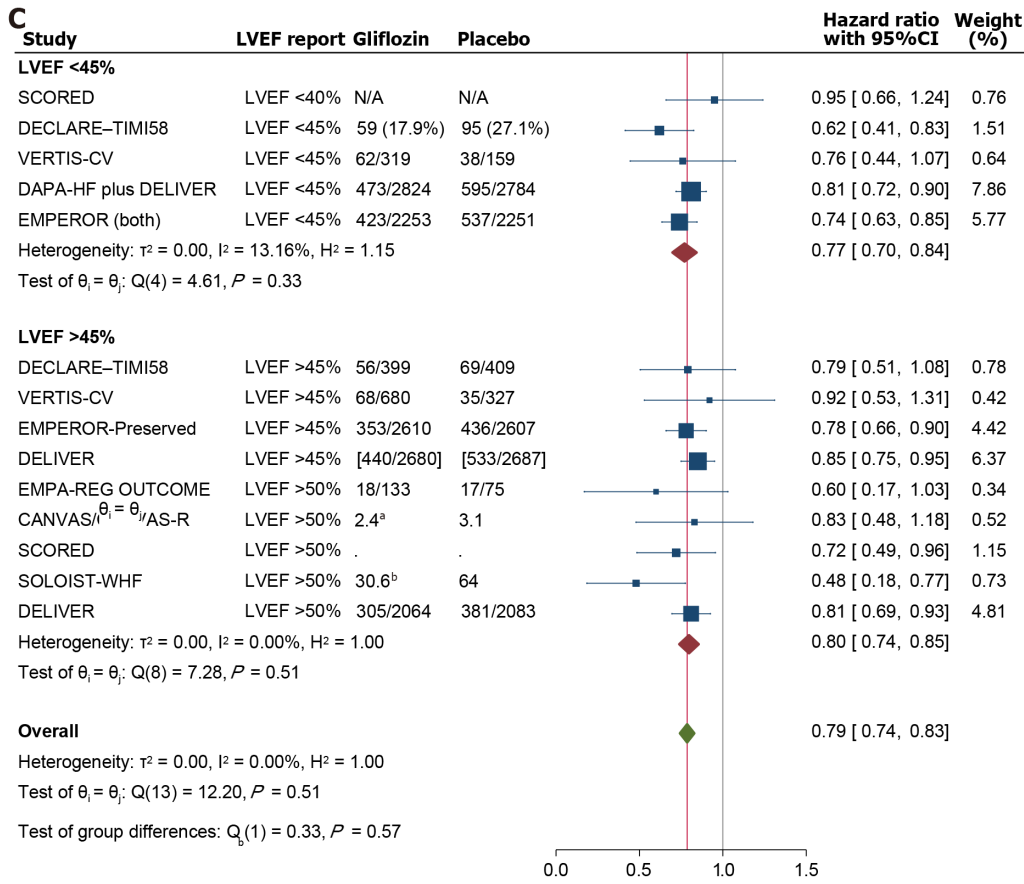
Renal disease progression or worsening renal function: Gliflozins significantly reduced renal disease progression in the meta-analysis (HR: 0.63, 95%CI: 0.55 to 0.71). But unlike the composite renal event, no significant difference was found regarding the heart failure status or across subtypes ($P = 0.52$; **Supplementary Figure 6**).

A

Random-effects DerSimonian–Laird model

B

Random-effects DerSimonian–Laird model



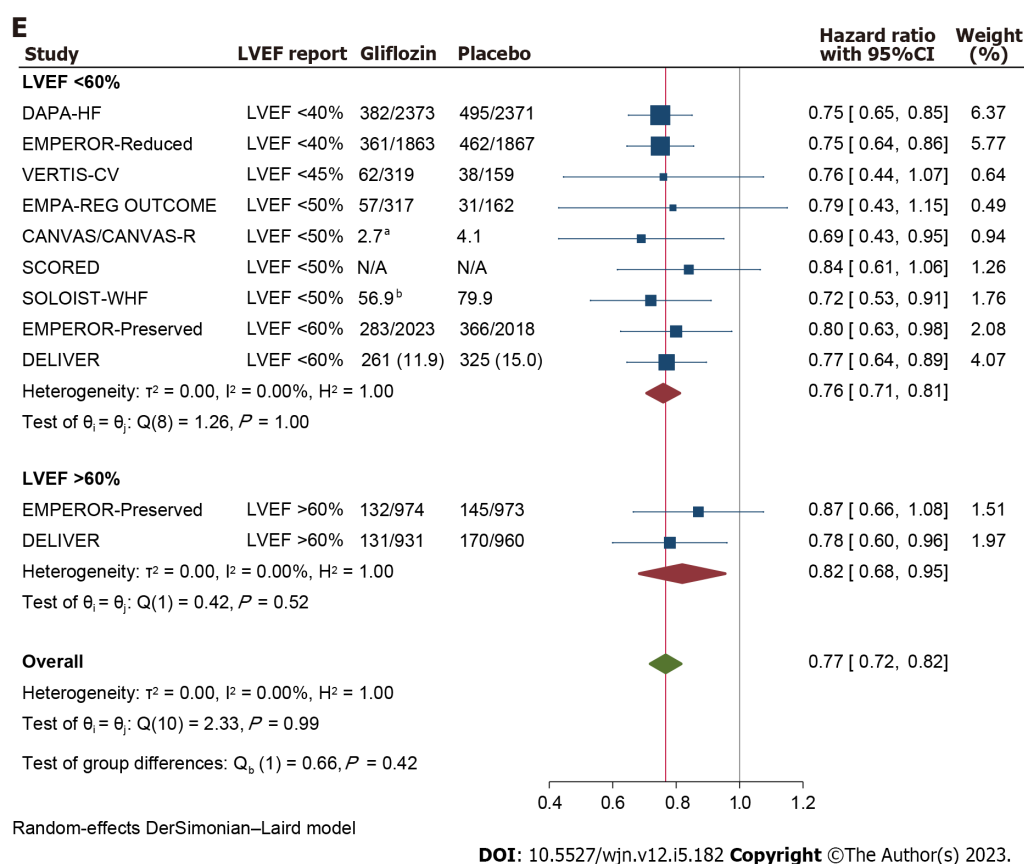


Figure 5 Meta-analysis of Sodium glucose cotransporter 2 inhibitors' effect on 'cardiovascular death or heart failure hospitalizations or urgent visits' across the patients' baseline left ventricular ejection fraction strata. A: Left ventricular ejection fraction (LVEF) < 30% vs $\geq 30\%$; B: LVEF < 40% vs $\geq 40\%$; C: LVEF < 45% vs LVEF $\geq 45\%$; D: LVEF < 50% vs LVEF $\geq 50\%$; E: LVEF < 60% vs LVEF $\geq 60\%$. ^aper 1000 person-years; ^bper 100 person-years; ^aanalysis based on the "history of previous LVEF < 40%" reported by DELIVER trial; LVEF: Left ventricular ejection fraction; N/A: Not available.

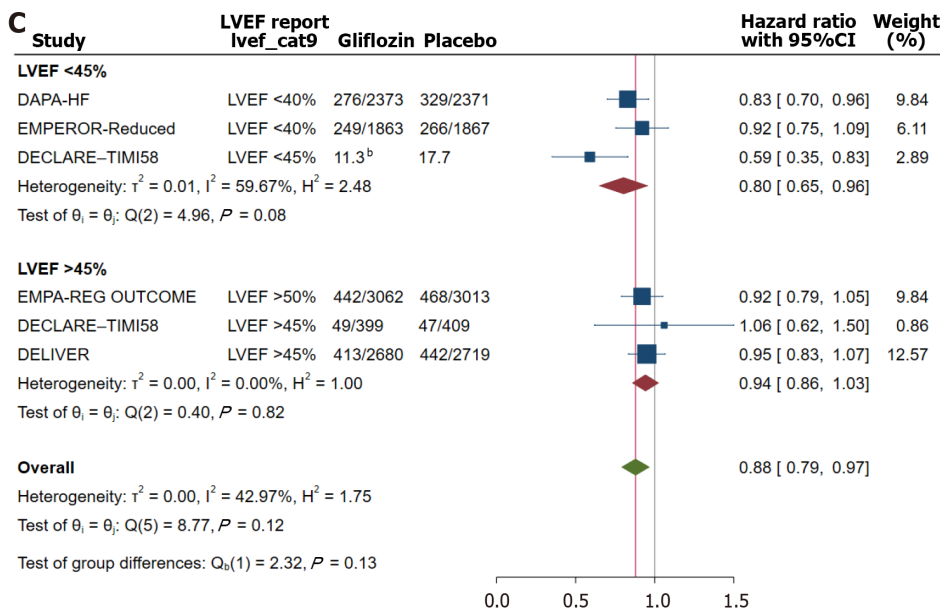
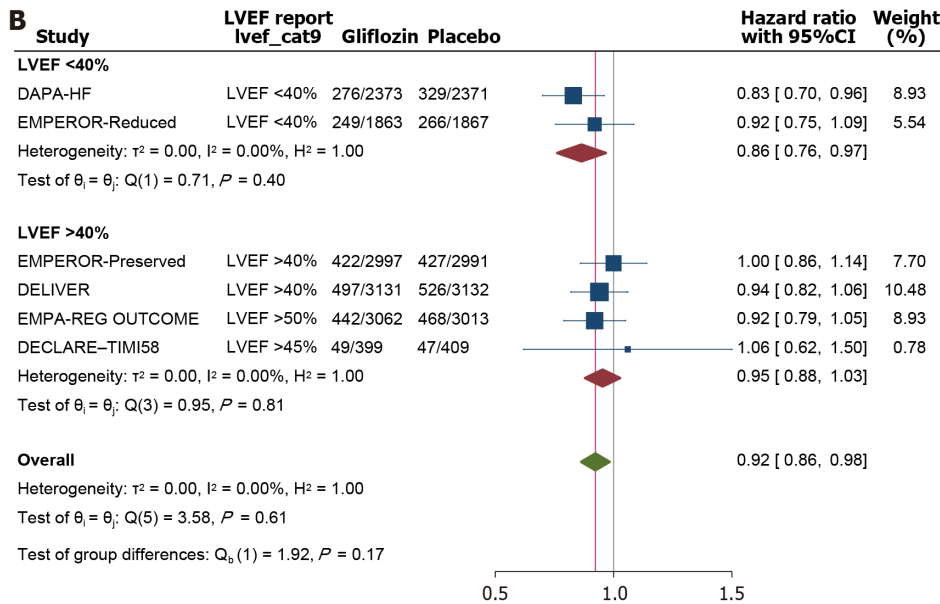
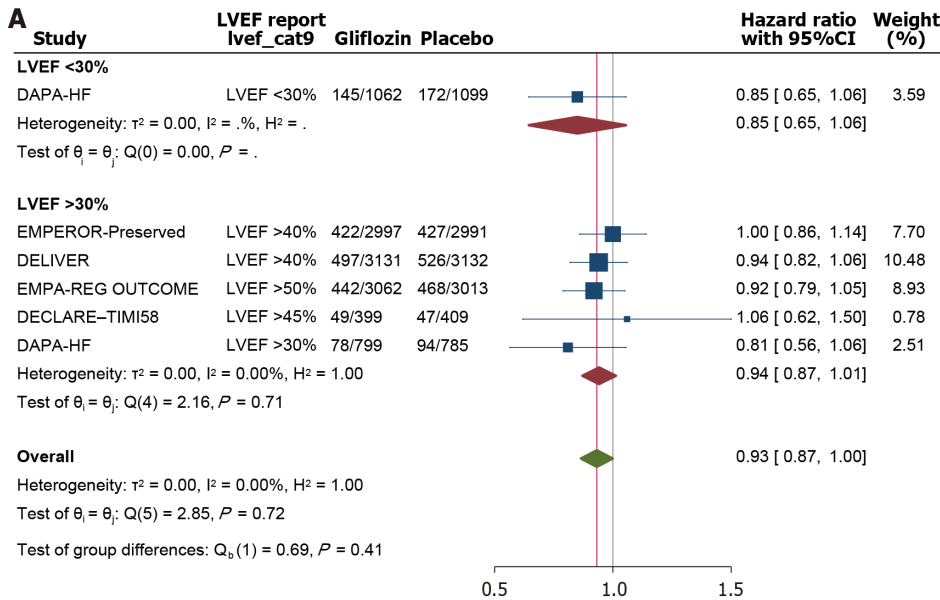
Volume depletion: As is evident from [Supplementary Figure 7](#), SGLT2i therapy was associated with significantly higher rates of volume depletion in the pooled data meta-analysis with no significant difference across the study subgroups (HR: 1.14, 95%CI: 1.02 to 1.26; $P = 0.33$).

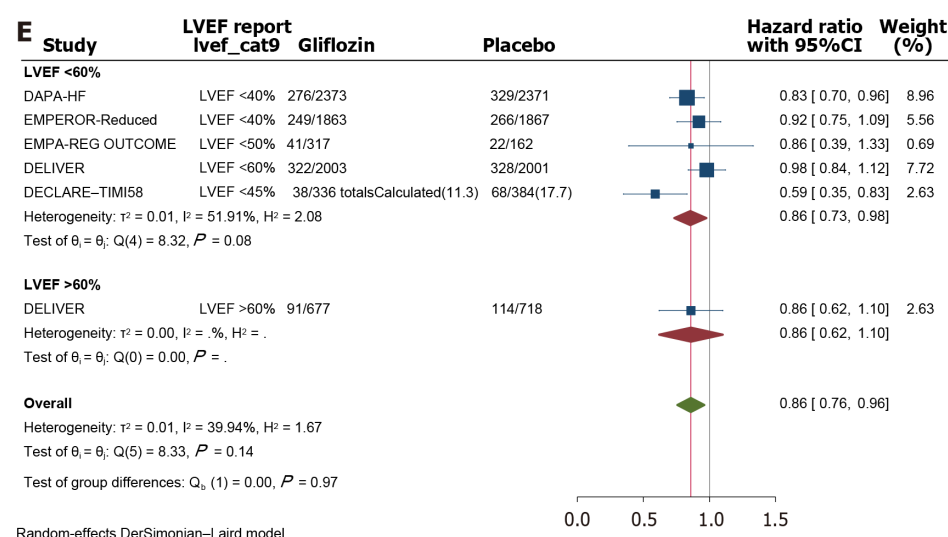
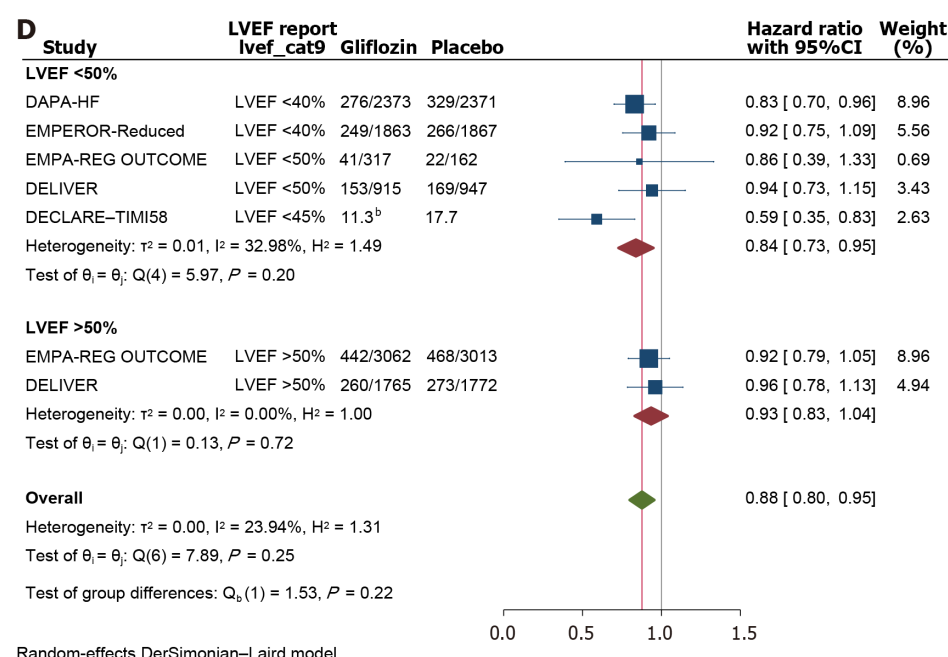
Diabetic ketoacidosis: As is summarized in [Supplementary Table 1](#), diabetic ketoacidosis was a rare observation in both the SGLT2i and placebo groups, and therefore meta-analyses were not possible. The distribution of the outcomes between the two groups reveals no heterogeneity.

DISCUSSION

In this meta-analysis of 13 large clinical trials, data of 45918 patients were screened and significant but inequivalent protective effects for SGLT2i were found across the patients' LVEF strata, regarding a spectrum of cardiovascular and renal outcomes. Compared to HFpEF patients, HFrEF exhibited more dramatic response to gliflozins in a good number of the predefined outcomes. This finding is in contrast to a previous study in which authors found equivalent efficacy in heart failure patients across a full spectrum of LVEF[30]. One reason for this disparity could be related to the number of studies and patients entered into the analysis, with the current study encompassing substantially larger population (including data from the mentioned study). As well, in the current study the analyses were performed across different cutoff points compared to the analyses across the spectrum of LVEF, which leaves only a limited number of subjects for each subgroup. Moreover the spectrum of specific outcomes investigated in the current study was relatively broader.

Previous review articles have explored several predicting factors on response to SGLT2i. In a comprehensive review, Baigent *et al*[20] analyzed the impact of diabetes mellitus on the cardiorenal protective effects of SGLT2i treatment and found no disparity regarding diabetes status. In another review study, Zelniker *et al*[2] reported that the cardiovascular benefits of gliflozins in diabetic population seem to be largely confined to patients with established atherosclerotic cardiovascular disease. Bhatia *et al*[34] provided evidence for SGLT2i protective effects in a broader range of cardiac, renal and metabolic derangements, and in another very recent *post hoc* analysis from DELIVER trial, Peikert *et al*[35] reported substantial improvements in a large range of symptoms, functionality indices, and quality of life in HFmrEF/HFpEF patients in response to SGLT2i. The current systematic review provides further data on the variability of response





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Figure 6 Meta-analysis of gliflozins' effect on the all-cause mortality across left ventricular ejection fraction strata (versus placebo). A: Left ventricular ejection fraction (LVEF) $\leq 30\%$ vs $> 30\%$; B: LVEF $\leq 40\%$ vs $> 40\%$; C: LVEF $\leq 45\%$ vs LVEF $> 45\%$; D: LVEF $\leq 50\%$ vs LVEF $> 50\%$; E: LVEF $\leq 60\%$ vs LVEF $> 60\%$. ^bper 100 person-years. LVEF: Left ventricular ejection fraction; N/A: Not available.

to gliflozins in heart failure patients regarding their LVEF levels and NYHA classifications, which could have significant clinical implications for the practitioners.

It is noteworthy that all the clinical trials reviewed in this study have compared the outcome of patients receiving gliflozins *vs* placebo. Although this verifies favorable effects for the drug, it doesn't provide robust evidence that this protective effect outweighs the advantages that are expectable from conventional medications prescribed in this patients; therefore it is still an open question as to whether or not gliflozins' protection outweighs the conventional medications or is there some sort of synergistic relationship between them. But this was out of the scope of the current systematic review, and future studies are required to issue this questions.

Cardiac outcomes: Gliflozins significantly improved the primary composite outcome of cardiovascular death and hospitalizations in patients with or without heart failure and across all the subgroups. However this effect seemed to be skewed in favor of HFpEF compared to HFpEF (the number of patients needed to be treated to save one additional patient from the primary composite outcome in the HFpEF was twice as large as the HFpEF in CANVAS/CANVAS-R trial[22] and 2.9 times for EMPEROR-Reduced *vs* either EMPEROR-Preserved or DELIVER[16,18]; this result was not reproduced in EMPA-REG OUTCOME trial[21]). Reanalyses of the patients' composite outcomes as described above (*i.e.* cardiovascular death or associated hospitalizations) were based on arbitrary definitions of heart failure subgroups by LVEF levels, inconsistently made by the authors in the different trials; therefore in order to have more precise conclusions, definitive cutoff points across LVEF were set and sought for the evaluation of the outcome, and it has been revealed that for a

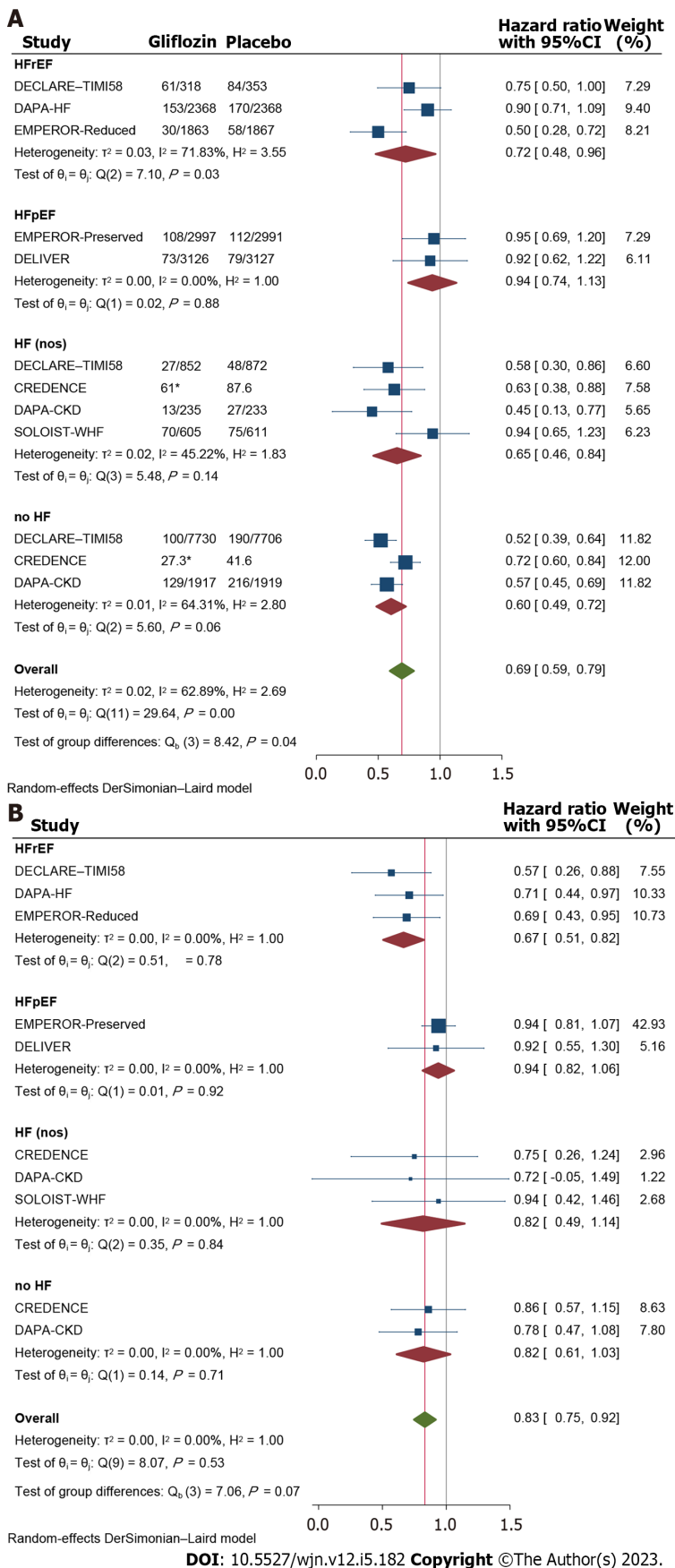


Figure 7 Meta-analysis of the Sodium glucose cotransporter 2 inhibitors' effect on different renal outcome indices across heart failure subtypes. A: Composite renal outcome; B: Acute kidney injury. HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; nos: Not otherwise specified.

Table 1 Summary of the reviewed trials

Ref.	Ref. post-hoc	Trial	Year	Follow (yr)	N	Participants	Diabetes proportion %	Heart failure proportion (%)	SGLT2i	Primary outcome
[7]	21	EMPA-REG OUTCOME	2015	3.1	7020	T2DM with established CVD; eGFR ≥ 30 mL/min/1.73 m ²	7020 (100)	706 (10)	Empagliflozin	CV death+non-fatal MI+non-fatal stroke
[8]	22	CANVAS/CANVAS-R	2017	2.4	10142	T2DM with CVD or multiple RFs for CVD; eGFR ≥ 30 mL/min/1.73 m ²	10142 (100)	1461 (14)	Canagliflozin	CV death+non-fatal MI+non-fatal stroke
[9]	23	DECLARE-TIMI58	2019	4.2	17160	T2DM with CVD or multiple RFs for CVD	17160 (100)	1724 (10)	Dapagliflozin	CV death+MI+ischemic stroke
[10]	24	VERTIS-CV	2020	3.5	8246	T2DM with established CVD; eGFR ≥ 30 mL/min/1.73 m ²	8246 (100)	1958 (24)	Ertugliflozin	CV death+non-fatal MI+non-fatal stroke
[11]	25	CREDENCE	2019	2.6	4401	T2DM with CVD+albuminuria (uACR 300–5000); eGFR 30–90 mL/min/1.73 m ²	4401 (100)	652 (15)	Canagliflozin	ESKD, doubling of serum creatinine/death from renal/CV cause
[12]	26, 27	DAPA-CKD	2020	2.4	4304	CVD + albuminuria +/- T2DM (eGFR 25–75 mL/min/1.73 m ²)	2906 (68)	468 (11)	Dapagliflozin	ESKD, sustained $\geq 50\%$ eGFR decline, death from renal or CV cause
[13]	-	SCORED	2020	1.3	10584	T2DM with CVD & RFs for CVD; (GFR) of 30 to 60 mL/min/1.73 m ²	10 584 (100)	3283 (31)	Sotagliflozin	CV death and hospitalizations and urgent visits for HF
[14]	28, 29	DAPA-HF	2019	1.5	4744	HF (EF $\leq 40\%$ & NYHA class II–IV) +/- T2DM; eGFR ≥ 30 mL/min/1.73 m ²	2139 (45)	4744 (100)	Dapagliflozin	Worsening HF and CV death
[15]	31	EMPEROR-Reduced	2020	1.3	3730	HF (EF $\leq 40\%$ & NYHA class II–IV) +/- T2DM	1856 (50)	3730 (100)	Empagliflozin	Composite of HF hospitalization and CV death
[16]		EMPEROR-Preserved	2021	26.2 months	5988	HF (EF $> 40\%$ & NYHA class II–IV) +/- T2DM; eGFR ≥ 20 mL/min/1.73 m ²	2938 (49)	5988 (100)	Empagliflozin	Composite of cardiovascular death or hospitalization for HF
[17]	32	SOLOIST-WHF	2020	0.75	1222	T2DM & recent hospitalization for HF; eGFR ≥ 30 mL/min/1.73 m ²	1222 (100)	1222 (100)	Sotagliflozin	CV death and hospitalizations and urgent visits for HF
[18]	30	DELIVER	2022	2.3	6263	HF (EF $> 40\%$ & NYHA class II–IV) +/- T2DM	3150 (50)	6263 (100)	Dapagliflozin	Hospitalization for HF or an urgent visit for HF or CV death
[19]		EMPA-KIDNEY	2023	2.0	6609	CKD [eGFR > 20 & < 45 OR $45 < eGFR < 90$ mL/min/1.73 m ² & (proteinuria)]	3040 (46)	658 (10)	Empagliflozin	eGFR to < 10 OR decrease in eGFR of $\geq 40\%$ OR renal death

CKD: Chronic kidney disease; CV: Cardiovascular; CVD: Cardiovascular disease; EF: Ejection fraction; eGFR: Estimated glomerular filtration rate; HF: Heart failure; MI: myocardial infarction; NYHA: New York Heart Associations classification of heart failure; RF: Risk factor; T2DM: Type 2 diabetes mellitus; SGLT2i: Sodium glucose cotransporter 2 inhibitors; NYHA: New York Heart Associations.

number of major outcomes, the benefit from SGLT2i therapy reaches significant difference in favor of the patients with lower LVEF, at the cutoff point of 30% (Supplementary Figure 4 and Figure 5). Interestingly, repeating the meta-analysis across NYHA classifications showed significantly enhanced therapeutic effects for patients at lower *vs* higher NYHA subclasses. These findings broaden our understanding on the subgroups of the heart failure patients who are likely to benefit most from the SGLT2i.

Death outcomes: Meta-analysis of the impact of SGLT2i on cardiovascular death and all-cause mortality also exhibited benefit with relative but none-significant difference between the subgroups (Figures 3 and 6 and Supplementary Figure 3). No significant survival benefit was detected for patients with HFpEF or in meta-analysis of data from patients with LVEF over 40%. For patients with HFmrEF, gliflozins failed to improve all-cause mortality but improved cardiovascular death just at the borderline significance (Figure 3 and Supplementary Figure 3). This findings rule out SGLT2i as a life-saving medication for HFpEF, and adds it to the list of drugs that have failed to extend life in these tough-to-treat patient population.

Renal specific outcome: Renal outcomes are of special interest in patients with either heart failure or diabetes mellitus and a main focus of attention in most of the reviewed trials. Although previous systematic reviews have shown the benefits of SGLT2i on renal events[20], potential variability in the magnitude of this protection across LVEF rates could have clinical implications. Interestingly, results of the meta-analysis of composite renal outcomes were consistent with the respective analyses on the cardiovascular outcomes, with the HFmrEF patients responding relatively but not significantly better to the treatment than HFpEF, though with an unexpected finding of detecting the most pronounced renal protective effects in patients without heart failure (Figure 7A). This offers that gliflozins' renoprotective effects are unlikely to be associated with their heart failure modifying effects and deserves further investigations.

In the meta-analyses of more specific renal outcomes, acute kidney injury was reduced by 32% in patients with HFmrEF compared to only 6% in HFpEF, a difference that was statistically significant (Figure 7B). On the other hand, not every specific renal outcome benefited by SGLT2i, and volume depletion had been shown to be significantly exacerbated by 14% compared to patients receiving placebo. This finding warns of the possible risks to patients receiving gliflozins and emphasizes the need for close monitoring of patients for signs of volume depletion.

Limitations and strengths: There are strengths and limitations associated with this study that warrants further discussion. Different patient populations (exclusive inclusion of patients with diabetes mellitus, chronic kidney disease or heart failure, or variations in the proportions of these patients in different studies), large variations in the follow up times, and inconsistencies in the outcome definitions and reports between the reviewed trials are a number of limitations that could undermine the findings of this study. The principle strength of the current systematic review is providing a stratified outcome analysis across the LVEF strata of patients with heart failure, and introducing the patient subgroups that are most or least likely to benefit from treatment with gliflozins. Identifying the patient populations that don't benefit the treatment gives a message to the scientific community that further research and developments are needed.

CONCLUSION

In conclusion, compared to placebo, SGLT2i have shown significant therapeutic effects in patients with or without heart failure regarding cardiovascular and renal outcomes. These effects are generally more pronounced in HFmrEF patients at the lowest LVEF levels compared to HFpEF, with no survival advantage for the latter group. Patients with lower NYHA classifications were also found to respond more vigorously to the study drugs. Further well-designed studies are needed to determine other potential factors with significant roles in response to gliflozins.

ARTICLE HIGHLIGHTS

Research background

Gliflozins have been shown effective to improve outcomes in patients with heart failure.

Research motivation

Finding the indications for the prescription of gliflozins would help to concentrate research on subgroups that need further research and novel therapeutic approach.

Research objectives

To find the subpopulations of heart failure patients that benefit most from Sodium glucose cotransporter 2 (SGLT2) inhibitors based on their left ventricular ejection fraction levels.

Research methods

A systematic review and meta-analysis of data of patients receiving gliflozin therapy in large and robust randomized double-blind placebo trials was conducted. Meta-analyses were conducted after stratification of the patients based on their left ventricular ejection fraction (LVEF) levels.

Research results

Gliflozins were generally superior to placebo in improving composite outcome of patients with heart failure across LVEF levels. This therapeutic effects were more pronounced in patients with reduced LVEF and low New York Heart Associations classes. No survival benefit was detected for patients with preserved ejection fraction disease.

Research conclusions

Gliflozins are effective in improving the outcome in patients with heart failure.

Research perspectives

Further research would be needed to examine the magnitude of gliflozins' efficacy as well as its cost-effectiveness compared to the other therapeutic options in this patient population.

FOOTNOTES

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