ISSN 2220-6124 (online)

World Journal of *Nephrology*

Quarterly Volume 13 Number 1 March 25, 2024

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

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INDEXING/ABSTRACTING

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

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Quarterly

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

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

PUBLICATION DATE
March 25, 2024

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World J Nephrol 2024 March 25; 13(1): 89637

DOI: 10.5527/wjn.v13.i1.89637

ISSN 2220-6124 (online)

EDITORIAL

Renoprotective strategies

Vaia D Raikou

Specialty type: Urology and nephrology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Thongon N, Thailand

Received: November 7, 2023
Peer-review started: November 7, 2023
First decision: November 30, 2023
Revised: December 1, 2023
Accepted: December 26, 2023
Article in press: December 26, 2023
Published online: March 25, 2024

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Abstract

Kidney disease remains a condition with an increasing incidence, high morbidity and mortality associated with cardiovascular events. The incidence of end-stage renal disease is expected to increase. Despite of the technical improvement, dialysis never achieved a full clearance of the blood dialysis. Therefore, the demand for new renoprotective measures has never been greater. Here, we report new strategies for preventing renal damage.

Key Words: Renoprotection; Acute renal disease; Chronic renal disease; Pathophysiology

Core Tip: Renoprotection presents a wide field of approaches, including a strict control of blood pressure, diabetes mellitus management and a balanced nutritional therapy. New diagnostic measures using isolated cells on bedside and novel therapeutic strategies are developed in terms the renoprotection and reducing of kidney disease progression resulting in a decreased cardiovascular risk for morbidity and/or mortality in chronic kidney disease patients.

Citation: Raikou VD. Renoprotective strategies. *World J Nephrol* 2024; 13(1): 89637
URL: https://www.wjgnet.com/2220-6124/full/v13/i1/89637.htm
DOI: https://dx.doi.org/10.5527/wjn.v13.i1.89637

INTRODUCTION

Chronic kidney disease (CKD) is a common condition in which the renal function is gradually decreased in process of time. The declining renal function is a main risk factor for increased morbidity and mortality including the cardiovascular disease (CVD) and thend-stage of kidney disease (ESRD). Furthermore, despite the increased improvement, dialysis never achieved a full clearance of the blood. CKD is defined by the presence of some criteria, including one or more structural or functional abnor-

malities, such as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, urine albumin-to-creatinine ratio (UACR) > 30 mg/g or urine albumin excretion rate > 30 mg/24 h, urine sediment abnormalities and renal tubular disorders for more than3 mo[1,2].

Renal insufficiency is on the rise worldwide and it is reflected on costs, which must be covered by society. In Germany have been recorded 109031 cases in 2013 *vs* 60451 cases in 2003. Moreover, according to 2021 data, the prevalence of CKD in the United States is estimated equal to 15% (37 million adults), and older individuals (aged 65 years or more) more usually suffer from CKD comparatively to younger patients and in non-Hispanic Black people versus non-Hispanic White people or Asians[3]. CKD is usually underestimated and patient and physician awareness is observed to be low. In the ADD-CKD study of diabetic adults, primary care physician indentified only 22% of patients with stage 3–5 CKD as having CKD[4]. The potential role of both characteristics of CKD (eGFR < 60 mL/min/1.73 m^2 and UACR > 30 mg/g) on CKD progression, development of ESKD, CVD and mortality is also under appreciated[5,6]. Therefore, new renoprotective strategies are greatly required.

Renal damage is complex and frequently multi-factorial. A deep understanding of the underlying pathophysiological mechanisms could obtain the highlights of the acute and chronic renal injury[7]. Environmental factors including metabolic, haemodynamic perturbations[8] and drugs in combination with a genetic susceptibility promote the activation of pro-oxidative, pro-inflammatory[9] and pro-fibrotic underlined pathophysiological mechanisms[10]. The acute renal disease is closely related to the primary injury, whereas in chronic renal disease may contribute common pathways including elevated levels of reactive oxygen species, activation of protein kinase Cβ, promotion of transforming growth factorβ1, disorder of vascular growth factors (*e.g.* VEGF-A, angiopoietins), increased advanced glycation end products and adipocytokines. A such procedure results in increased extracellular matrix deposits, thickening of the glomerular basement membrane along with mesangial expansion. Finally, glomerular sclerosis is activated and tubulointerstitial fibrosis is elevated.

RENOPROTECTIVE APPROACHES

Current renoprotective therapies leave much space for innovation. Acute kidney insufficiency (AKI) can be slowed by volume loading before contrast media exposure. Nevertheless, current approaches targeting in specific mechanisms of disease are proved unsatisfactory and therapeutic options for treating AKI still fail to significantly improve outcomes. This may need basic research obtained by isolated cells and tissue preparation using animal models on the bedside.

In CKD, one of the major renoprotective strategy may be the strict control of hypertension, a common disorder in renal disease population. In the last 20 years, the only categories of recommended agents for diabetic or non-diabetic patients with CKD and hypertension, were angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) mainly in terms of reducing albuminuria caused by the reduction of glomerular hypertension[2]. The usage of low dietary sodium is often overlooked, but can improve BP control, especially for patients treated with the above reported agent, which blocks the renin-angiotensin system. The effect of diuretics on cardiovascular morbidity and mortality has been previously established. Chlorthalidone therapy improved blood-pressure control at 12 wk among patients with advanced CKD and poorly controlled hypertension[11,12]. Hypokalemia, hyperglycemia and hyperuricemia more frequently occurred in the group of patients with chlorthalidone compared to control group. However, hypokalemia is considered to be a desired condition in CKD patients.

Renal disorders are common in diabetics and an analysis of the United States Diabetes Collaborative Registry revealed that 20% of diabetic patients presented CKD[13]. The progression of diabetic nephropathy in patients with T2D treated with angiotensin receptor blockers was estimated to be closed to 15%–27% comparatively to placebo-treated patients over 2 years, depending on the level of baseline risk[14]. Moreover, the improved control of both hyper-glycemia and hypertension and the usage of renin–angiotensin system blockers did not achieve to protect the kidney function of people with T2D[15]. Evidence is now accumulating to suggest some drugs to be potential treatments for chronic kidney disease, even though these initially were developed to treat other diseases. The sodium–glucose cotransporter 2 inhibitors, which are commonly used to lower blood sugar levels in diabetic patients, are examples of such drugs. SGLT2 inhibitors reduced the risk of deterioration of renal outcomes (permanent loss of kidney function, eGFR decline, worsening of albuminuria, new ESKD, and death from renal causes) additionally to significant reduction of cardiovascular events risk than plasebo, indicating that SGLT2 inhibitors are associated with significantly lower risk of deterioration of kidney function, due mainly to reducing of glomerular hypertension and hyperfiltration[16,17]. However, the initial studies were enclosed only 7%–26% of participants who had an eGFR less than 60 mL/min/1.73 m^2 and could not evaluate treatment benefits in patients with CKD[16,17]. Secondarily, newer trials showed a significant reduction in the risk of CKD worsening with SGLT2 inhibitors in patients with diabetic kidney disease using canagliflozin in CREDENCE[18] and diabetic as well as nondiabetic CKD using dapagliflozin in DAPA-CKD[19]. More recently, EMPA-KIDNEY trial showed that empagliflozin therapy resulted in a lower risk of progression of kidney disease or death from cardiovascular events compared to placebo, enrolling patients with a high risk for renal disease progression[20].

Increased plasma aldosterone levels have been reported to be a main risk factor for renal injury and it could be improved by mineralocorticoid receptor (MR) antagonist therapy[21]. Renal endothelial dysfunction characterized by inflammatory activation, impaired vasodilation and fibrosis were induced by MR activation. MR-mediated glomerulosclerosis may decrease the ability of capillary oxygen offer, which could finally lead in ischemic renal injuries[22]. MR blockers (spironolactone and eplerenone) may attenuate the declined eGFR and severity of histopathological lesions resulting to an eventual protection of the patients from potential ischemic renal injuries and proteinuria. Novel, selective, nonsteroidal MR antagonists (finerenone, esaxerenone) have demonstrated therapeutic efficacy not only in hypertensive

patients but also in diabetic patients with microalbuminuria leading these drugs to be the choice of medical therapy in CKD patients compared to steroid MR antagonists[23-25]. Moreover, it has been shown that aldosterone blockade with renin-angiotensin-aldosterone system inhibitors, such as ARBs, is renoprotective reducing albuminuria independently on control of hypertension[26]. Another new class of medication, aldosterone synthase inhibitors, which reduces aldosterone production by inhibiting aldosterone synthase shows promise on slowing of renal injury progression[27].

Metabolomics has been demonstrated to be potential for identifying the mechanisms of underlying disease, facilitating clinical diagnosis and developing pharmaceutical treatments for CKD. It was revealed by recent research in metabolomics that CKD was significantly associated with the disorder of many metabolites, such as amino acids, lipids, nucleotides and glycoses. These might be important biomarkers inducing new targets for CKD treatment and renoprotection[28].

During renal injury the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is elevated and an imbalance of ROS and RNS generation and excretion leads to inflammation, cell death, tissue injury and kidney disease progression[29]. In combination with chronic inflammation, the increased oxidative stress and malnutrition are associated with CKD and increased cardiovascular risk. Hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C), which are the main lipidemic disorders in CKD, are major risk factors for CVD[30]. It has been shown that dyslipidemia and lipid deposition in the kidneys over time worsen kidney function by causing damage to endothelial cells, mesangial cells, and glomerular podocytes, due to the activation of inflammatory cascade. Studies indicate that dietary polyunsaturated fatty acids might delay the onset of CKD and attenuate CVD and kidney disease progression[31]. It has been shown that treatment with statin can decrease CV events in patients with pre-end-stage CKD and in renal transplant patients, but not in those with end stage of renal disease[32]. Peroxisome proliferator-activated receptor-alpha (PPARα) levels are significantly lower in patients with CKD. Fibrates, which are PPARα agonists, are therapeutic agents against hypertriglyceridemia and these could also protect renal function. However, conventional fibrates are decreased by renal metabolism, reducing their use in patients with impaired renal function. Recently, using mice in CKD it has been shown the renoprotective effects of pemafibrate, a novel selective PPARα modulator which is mainly excreted into the bile[33].

Moreover, previous study indicated that melatonin administration for 12 wk in diabetic nephropathy patients had beneficial effects on glycemic control, HDL-C, total antioxidant capacity and glutathione levels, and gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ)[34]. Recent study investigated if melatonin-stimulated mesenchymal stem cells (Exocue) secret exosomes with therapeutic effects on the improvement of kidney function in a CKD mouse model and it was indicated that Exocue could regulate inflammation and fibrosis and it could be a novel therapeutic agent for treating CKD[35].

An additional renoprotective approach in CKD would be the regulation of metabolic acidosis and hyperkalemia, common characteristics in these patients. Previously, we have demonstrated that patients with low bicarbonate level should be treated properly even though they are receiving dialysis therapy due to metabolic acidosis results in detrimental effects[36]. It has already been reported the role of metabolic acidosis on vascular calcification and renal progression, due mainly to promotion of inflammation in arterial wall, releasing cytokines[37]. Increased intake of proteins leads to the production of increased load of acids due to degradation of proteins resulting in rapid decline of kidney function. Therefore, low protein diet, particularly from plant sources, may have beneficial effects on kidney function due to metabolic acidosis attenuation in CKD[38], despite it has been also reported that higher intake of total protein was associated with a lower risk of cardiovascular morbidity[39]. In patients with CKD hyperphosphatemia is a potential risk factor for cardiovascular disease and bone disorders. Because of 1 gr of protein contains about 13 mg phosphorus, protein-rich foods are the main natural source of phosphorus intake. Such a result low protein diet could be effective for the management of hyperphosphatemia and renal and cardiovascular protection. The low serum phosphorus is associated with reductions in serum levels of parathyroid hormone and fibroblast growth factor 23 leading to a slow progression of vascular calcification, delayed worsening of renal function and improving cardiovascular outcomes[40].

CONCLUSION

We could conclude that renoprotection presents a wide field of approaches, including a strict control of blood pressure, diabetes mellitus management and a balanced nutritional therapy. In the modern era, new diagnostic measures using even isolated cells and novel therapeutic strategies are developed in terms the renoprotection and reducing of kidney disease progression resulting in a decreased cardiovascular risk for morbidity and/or mortality in CKD patients.

FOOTNOTES

Author contributions: Raikou VD contributed tostudy design, data collection, manuscript preparation, literature search.

Conflict-of-interest statement: All the author declares no conflict of interests.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao S

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World Journal of Nephrology

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

World J Nephrol 2024 March 25; 13(1): 90542

DOI: 10.5527/wjn.v13.i1.90542

ISSN 2220-6124 (online)

EDITORIAL

Point of care ultrasonography as the new "Laennec Sthetoscope"

Ernesto Sabath

Specialty type: Medicine, general and internal

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Munasinghe B, Sri Lanka

Received: December 7, 2023
Peer-review started: December 7, 2023
First decision: December 31, 2023
Revised: January 19, 2024
Accepted: February 29, 2024
Article in press: February 29, 2024
Published online: March 25, 2024

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Abstract

Point of care ultrasonography (POCUS) has evolved to become the fifth pillar of the conventional physical examination, and use of POCUS protocols have significantly decreased procedure complications and time to diagnose. However, lack of experience in POCUS by preceptors in medical schools and nephrology residency programs are significant barriers to implement a broader use. In rural and low-income areas POCUS may have a transformative effect on health care management.

Key Words: Point-of care ultrasonography; Central venous catheter; Internal medicine; Obstetric emergencies; Medical training

Core Tip: Point of care ultrasonography (POCUS) has become an important tool in patient care. POCUS protocols has reduced complications in invasive procedures and improved diagnostic times. In rural and low-income areas POCUS have an important role on health care management.

Citation: Sabath E. Point of care ultrasonography as the new "Laennec Sthetoscope". *World J Nephrol* 2024; 13(1): 90542
URL: https://www.wjgnet.com/2220-6124/full/v13/i1/90542.htm
DOI: https://dx.doi.org/10.5527/wjn.v13.i1.90542

INTRODUCTION

Point of care ultrasonography (POCUS) it is defined as a focused ultrasound examination performed by any physician at the patient's bedside, allowing immediate and correct clinical integration[1]. A clinician uses POCUS to guide the evaluation and

diagnosis in conjunction with a traditional medical examination; in fact, POCUS has evolved to become the fifth pillar of the conventional physical examination (inspection, palpation, percussion, auscultation, and ultrasonography)[2].

As was elegantly described by Koratala *et al*[3] in his review about myths, POCUS emerges as a useful tool for any nephrologist, and helps to answer specific clinical questions such as "Does this patient with left side pain have kidney stones?" or "Does this patient with recently diagnosed abnormal creatinine levels have small kidneys?".

POCUS allows the physician to review and interpret images and make critical decisions at the point of care, and many studies have shown that POCUS protocols significantly reduced diagnostic time[4], decrease procedure complications[5], improves patient safety, increased success rates of invasive bedside procedures[6], and minimize delays in care such as time to obtain antibiotics or time to move into surgery[7].

One of the biggest barrier to the widespread use of POCUS has been the lack of adequate training curricula in undergraduate and specialty courses[8]. Koratala *et al*[3] describe that 73.8% of United States undergraduate medical schools have integrated POCUS into basic science courses; however, even in other developed countries this percentage is lower (in Canada and according to the 2014 census only 50% of the medical schools included it as part of their curricula[9]), and in developing nations the information is almost non-existent.

Even though there is a solid evidence that POCUS implementation improves the traditional examination techniques and that is very clear that POCUS is essential to the nephrology practice, still few nephrology programs in Latin-America (LA) and other regions introduce POCUS as curricular training[10]; the inexperience of preceptors in these courses is an important limitation in these countries[11]. Current training programs are heterogeneous without rigorous quality control; short-term courses are useful to initiate POCUS training but practice and learning curricula should span the entire nephrology residency[12].

Also, the unavailability of ultrasound machines (USM) still precludes its use in low-socioeconomic countries; in one study conducted in intensive care units from Sri Lanka, lack of USM availability delayed 80% of interventions and optimal management[13]. However, the introduction of low-cost and more portable ultrasound models in the health-market will surely diminish this shortage in the near future.

The percentage of nephrologist interested in learning POCUS is high (95% in a recent Brazilian-survey), although most of them think in POCUS as a help for central venous catheters placement and not as a guide to do volume assessment, lung evaluation, *etc*[14].

Lack of time was also considered as one of the most important barriers for POCUS implementation and learning in almost every country[15]; however some studies have shown that even short courses (*i.e.* a 16-h training course) covering topics associated with complications of kidney disease in lung, heart, *etc.* can be helpful to develop POCUS skills in clinical practice[12], but as mentioned before must be completed with further training.

POCUS is becoming a widely useful tool in low- and middle- income countries due to its portable nature, trainable interface and readily available data to guide clinical decision-making, and has been widely demonstrated its utility in rural and remote areas with no access to other diagnostic methods[16].

Studies performed in poorer regions of Mexico have shown that ultrasound changed the management plan in 30% of patients[17]. As expected, most of ultrasounds performed in rural and low-income areas are done as help in gynecologic-obstetric problems and is an important tool to provide adequate imaging in screening for placenta *previa*, fetal malposition, multiple gestations, ectopic pregnancy, *etc*[18]. This experience has been replicated in another low-income countries such as Uganda, Malawi, Tanzania[19], *etc.* As ultrasound machines become more portable and affordable, coupled with increasing capacity to transmit digital images for remote review, the introduction of POCUS may have a transformative effect on health care in resource-limited settings.

Another barrier in many countries (*i.e.* LA countries) is the lack of non-english literature and publications: a recent PUBMED search found less than 30 papers in Spanish about POCUS and less than 10 searching with the terms "POCUS", "riñón", "nefrologia"[20].

CONCLUSION

Many efforts has to be done to increase POCUS training in residency programs outside of the United States; availability of pocket ultrasound is not a limitation as they are of good quality and not so expensive. We have to take out the fear that POCUS is going to limit our clinical abilities and to impair the doctor-patient relationship, we have to think in POCUS as the new "Laennec stethoscope"[21] that is going to help us to make more accurate diagnosis and to improve the patient care.

FOOTNOTES

Author contributions: Sabath E collected the literature, analyzed the data, wrote the draft and revised and submitted the manuscript.

Conflict-of-interest statement: The author declares no competing interests.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao S

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World Journal of Nephrology

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

World J Nephrol 2024 March 25; 13(1): 88967

DOI: 10.5527/wjn.v13.i1.88967

ISSN 2220-6124 (online)

OPINION REVIEW

Challenges with non-descriptive compliance labeling of end-stage renal disease patients in accessibility for renal transplantation

Benjamin Peticca, Tomas M Prudencio, Samuel G Robinson, Sunil S Karhadkar

Specialty type: Medicine, general and internal

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Salvadori M, Italy

Received: October 16, 2023
Peer-review started: October 16, 2023
First decision: November 14, 2023
Revised: November 22, 2023
Accepted: December 22, 2023
Article in press: December 22, 2023
Published online: March 25, 2024

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Abstract

Non-descriptive and convenient labels are uninformative and unfairly project blame onto patients. The language clinicians use in the Electronic Medical Record, research, and clinical settings shapes biases and subsequent behaviors of all providers involved in the enterprise of transplantation. Terminology such as *noncompliant* and *nonadherent* serve as a reason for waitlist inactivation and limit access to life-saving transplantation. These labels fail to capture all the circumstances surrounding a patient's inability to follow their care regimen, trivialize social determinants of health variables, and bring unsubstantiated subjectivity into decisions regarding organ allocation. Furthermore, insufficient Medicare coverage has forced patients to ration or stop taking medication, leading to allograft failure and their subsequent diagnosis of *noncompliant*. We argue that perpetuating non-descriptive language adds little substantive information, increases subjectivity to the organ allocation process, and plays a major role in reduced access to transplantation. For patients with existing barriers to care, such as racial/ethnic minorities, these effects may be even more drastic. Transplant committees must ensure thorough documentation to correctly encapsulate the entirety of a patient's position and give voice to an already vulnerable population.

Key Words: End-stage renal disease; Compliance; Labeling; Social determinants

Core Tip: For a very long time, patients with renal failure have had challenges to transplantation. Inequities in access to transplantation are widely apparent across diverse geographic zones. Increasing these disparities are non-descriptive labels that perpetuate stereotypes and further disadvantage minority populations. In this manuscript, we crystallize the roles of such labeling and seek to implore the Nephrology community to improve equity in organ transplantation.

Citation: Peticca B, Prudencio TM, Robinson SG, Karhadkar SS. Challenges with non-descriptive compliance labeling of end-stage renal disease patients in accessibility for renal transplantation. *World J Nephrol* 2024; 13(1): 88967
URL: https://www.wjgnet.com/2220-6124/full/v13/i1/88967.htm
DOI: https://dx.doi.org/10.5527/wjn.v13.i1.88967

INTRODUCTION

Over the past decade, a renaissance of patient-centered language has emerged, transforming terms such as “drug addict” and “diabetic” to "person who uses drugs" and "person with diabetes." Such language helps recast how healthcare teams, the public, and patients view their circumstances. Placing a person's humanity before their condition or diagnosis lends some much-needed context and empathy. Modern medicine is continuing to adapt, fixing past shortcomings, and shaping the future of clinical care. The enterprise of End-Stage Renal Disease (ESRD) care and kidney transplantation is no different. Here, we argue that patient-centered language is critical in transplantation as conscious and unconscious biases have more significant consequences when brought into decisions regarding organ allocation. Transplantation poses a distinct challenge, requiring a difficult balance between patient equity and utility when deciding how to ration a limited number of organs to an ever-growing list of candidates. When making these decisions, it is vital to understand each patient’s circumstance completely rather than rely on the convenient labels that have been perpetuated through decades of an evolving care system. The United Network for Organ Sharing (UNOS) database reports over 11.7 million instances where a patient was temporarily inactivated from the waitlist due to the use of non-informative language such as “work-up incomplete” and “medical noncompliance.” These reasons account for over 70% of all inactivations between 2006-2020. Such labels create bias in a field that requires a holistic evaluation of an ESRD patient’s viability for life-saving transplantation.

HOW DID WE GET HERE?

The term *compliance* was initially used to describe patients' obedience to physician advice. By the 1970s, *medical noncompliance* was used more narrowly to characterize patients unwilling or unable to take their prescribed medication. The newer term *nonadherence* offers a slightly less patronizing perspective, yet both terms contribute to a power imbalance between patient and physician[1]. While these terms are known to be potentially harmful, more neutral labels have surfaced in the field of nephrology and renal transplantation, such as *work-up incomplete*. We argue that the use of non-descriptive language fails to capture a patient’s real-world experience.

Non-descriptive terminology, in this context, is defined as a single word or phrase that does not correctly describe the totality of a patient's circumstance. All labels are fundamentally flawed in their ability to describe situations in detail. However, reliance on non-specific labels denies due process to the patient and overlooks potential mitigating factors in the patient’s situation. Importantly, replacing terms such as *nonadherence* or *noncompliance* with another label would be futile, further perpetuating the same inequities left by their use. Historically, as reviewed in Laederach-Hoffman and Bunzel, in 1997, The Royal Pharmaceutical Society of Great Britain recommended using the term "nonconcordance" to replace *noncompliance* without alluding to the systemic hierarchy in medicine[2]. Although the term was never adopted, it demonstrates a pattern of inappropriate change.

LIMITATIONS WITHIN KIDNEY TRANSPLANTATION

In reviewing the UNOS database, *work-up incomplete* accounted for 178578 patients being inactivated from the waitlist between 2006-2020. Although *work-up incomplete* is not stigmatizing, the term provides no added information besides the lack of data or patient-derived follow-up. We argue that labels, such as work-up incomplete, generalize patient situations. The more valuable Electronic Medical Record (EMR) information answers “what is incomplete” and, equally important, “why is it incomplete.” In situations where work-up incomplete is a label accurately used to describe missing patient information, such as a colonoscopy, the EMR should explicitly describe what is incomplete. A comprehensive EMR note may read, "work-up incomplete due to missing updated colonoscopy, as the patient is unable to afford transportation to the center." Thorough descriptions impart much-needed context and empathy with the hope of changing the treatment approach or plan. A culture change in patient documentation could expand the involvement of other care team members in addressing the needs of each patient.

THE PROBLEM

Terminology that attempts to describe a patient's inability to follow the care regimen does not account for social determinants of health such as medication cost, lack of family support, insufficient information, overwhelming numbers of medications, and others[2]. Not only are these nonspecific labels unable to encompass socioeconomic factors, but they also lend to dangerous provider assumptions that once a patient is labeled *noncompliant*, they will remain *noncompliant*. Understanding why patients receive these labels is essential to providing patient-centered healthcare that improves access and gives patients the care they deserve. Still, *noncompliance* remains a diagnosis in the EMR. While newer iterations of the International Classification of Diseases (ICD-10) coding system provide some ability to report additional descriptors, as seen in Table 1, these stigmatizing labels continue to inadequately portray patients' circumstances. Additionally, labeling has different consequences in different contexts. While the convenience of nonspecific terminology may offer some practicality in acute settings, convenience offers less value in deliberative processes such as organ allocation in ESRD.

These labels are also frequently used in the academic literature across various transplantation journals when characterizing the well-understood association between inconsistencies in taking medication and poor graft survival. Since 2000, 193 papers on PubMed have titles that reference *noncompliance* terminology within transplantation. These studies have found that patients who struggle to follow their immunosuppression regimen have an elevated risk of late allograft failure[2,3]. As a result, institutional transplant committees use patient *noncompliance* as a criterion for waitlist delisting. According to the UNOS Database, 7852 patients have been temporarily inactivated from the waitlist due to *medical noncompliance* between 2006 and 2020. Although it is not policy to preclude a patient from transplantation indefinitely once inactivated for these reasons, the added barrier to transplantation places an unfair toll on patients and their caregivers. When making decisions regarding waitlist modifications, patient records should reflect, in granular detail, the reasons for their inability to adhere to their care plan. Furthermore, patients should have the ability to contest these labels.

INSUFFICIENT INSURANCE COVERAGE

Insufficient Medicare coverage of immunosuppressive medication highlights an extenuating circumstance where nonspecific labels such as *noncompliant* do not accurately encapsulate a patient's behavior. In 2020, 59% of all adult kidney transplant recipients in the United States relied on Medicare as their primary insurance provider[4]. Unfortunately, since 1993, Medicare has only covered immunosuppressive drugs for the first 36 months following a kidney transplant in patients under 65 years old without work-related disabilities[5]. This abrupt cutoff of coverage forces a financial burden onto many patients, leading to the rationing or discontinuation of their medications and eventual allograft failure. In addition, patients who remained consistent with their immunosuppressive regimen until the expiration of their prescription coverage are mischaracterized as *noncompliant*. As a result of persistent advocacy, the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act of 2020 has made lifelong Medicare coverage of immunosuppression a reality in 2023[6]. Regardless, for patients who have already stopped or rationed their medications due to inadequate coverage, the damage is done.

Arguments for using non-descriptive labels, such as *noncompliance* or *nonadherence* stipulate that their use adequately reflects situations where patients are actively unwilling to follow the care regimen. While clinicians and researchers may believe that the selective use of these labels is justified, this opens the door for subjective and unfair labeling across the entire organ transplant recipient population. Non-descriptive language trivializes the reasons for *noncompliance* with no regard to medical and social factors that led to such behavior. The indiscriminate use of these labels without adequate explanation of the inability or unwillingness to follow the care regimen adds nothing but unsubstantiated subjectivity to decisions regarding life and death.

STIGMATIZING LANGUAGE AND RACIAL BIAS

Recent literature reports that EMR notes regarding Black patients are more likely to include stigmatizing language when compared to notes regarding White patients[7]. This supports the findings of many studies, which indicate that healthcare providers hold conscious or unconscious biases toward people of color[8]. Transplant clinicians are no exception, as racial discrimination has manifested throughout multiple areas of the renal transplant process. Compared to White patients, Black patients are less likely to be referred, evaluated, and approved for transplant, more likely to be excluded from the waitlist, and ultimately experience decreased rates of transplantation and retransplantation[9,10]. We argue that the increased use of stigmatizing language in minority populations plays a role in their diagnosis as *noncompliant*, reducing their access to transplantation.

CONCLUSION

Non-descriptive labels in transplantation are unfortunately common and unfairly project blame onto ESRD patients. Labels such as *noncompliance*, *nonadherence*, and *work-up incomplete* fail to accurately portray ESRD patients awaiting transplantation. The grave nature of the situation is compounded by their prevalence in literature and patient care over

Table 1 ICD-10-CM codes characterizing noncompliance diagnoses

Z91.1	Patient's noncompliance with medical treatment and regimen
Z91.11	Patient's noncompliance with dietary regimen
Z91.12	Patient's intentional underdosing of medication regimen
Z91.120	Due to financial hardship
Z91.128	Due to other reason
Z91.13	Patient's unintentional underdosing of medication regimen
Z91.130	Due to age-related debility
Z91.138	Due to other reason
Z91.14	Patient's other noncompliance with medication regimen
Z91.15	Patient's noncompliance with renal dialysis
Z91.19	Patient's noncompliance with other medical treatment and regimen

The Z91 category refers to "personal risk factors, not elsewhere classified" in the ICD-10-CM system (ICD-10-CM International Classification of Diseases-10th Revision-Clinical Modification).

the last two decades. Furthermore, implementing the ICD-10 coding system has streamlined portions of an overburdened EMR, yet it incompletely describes ESRD patients with barriers to care. Minority populations and those who rely on Medicare already experience existing challenges and deserve comprehensive language the most. National organ sharing networks should incorporate strict delisting criteria for prospective transplant recipients, eliminate non-descriptive terminology such as *noncompliance,* and work to limit bias and subjectivity throughout the allocation process. We urge providers, regardless of specialty, to report patient information in granular detail to ensure the entirety of the patient's circumstance is captured. We recognize the burden these actions place on clinicians. However, the convenience of using non-descriptive labeling grossly mischaracterizes patients' behavior, limiting their access to life-saving transplantation.

FOOTNOTES

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Author contributions: Peticca B and Prudencio TM contributed equally to this work; Peticca B, Prudencio TM, and Karhadkar SS designed the research study; Peticca B, Prudencio TM, Robinson SG, and Karhadkar SS participated in drafting the manuscript and critical manuscript revision. Peticca B and Prudencio TM performed data collection and statistical analysis; All authors have read and approved the final manuscript. Benjamin Peticca and Prudencio Tomas M contributed equally to this manuscript.

Conflict-of-interest statement: None of the authors have any conflict of interest to disclose.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao S

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World Journal of Nephrology

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

World J Nephrol 2024 March 25; 13(1): 88028

DOI: 10.5527/wjn.v13.i1.88028

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinicopathological features and medium-term outcomes of histologic variants of primary focal segmental glomerulosclerosis in adults: A retrospective study

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Specialty type: Urology and nephrology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Tanaka H, Japan

Received: September 6, 2023
Peer-review started: September 6, 2023
First decision: November 21, 2023
Revised: November 30, 2023
Accepted: January 11, 2024
Article in press: January 11, 2024
Published online: March 25, 2024

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Abstract

BACKGROUND

The Columbia classification identified five histological variants of focal segmental glomerulosclerosis (FSGS). The prognostic significance of these variants remains controversial.

AIM

To evaluate the relative frequency, clinicopathologic characteristics, and medium-term outcomes of FSGS variants at a single center in Pakistan.

METHODS

This retrospective study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan on all consecutive adults (≥ 16 years) with biopsy-proven primary FSGS from January 1995 to December 2017. Studied subjects were treated with steroids as a first-line therapy. The response rates, doubling of serum creatinine, and kidney failure (KF) with replacement therapy were compared between histological variants using ANOVA or Kruskal Wallis, and Chi-square tests as appropriate. Data were analyzed by SPSS version 22.0. *P*-value ≤ 0.05 was considered significant.

RESULTS

A total of 401 patients were diagnosed with primary FSGS during the study period. Among these, 352 (87.7%) had a designated histological variant. The not otherwise specified (NOS) variant was the commonest, being found in 185 (53.9%) patients, followed by the tip variant in 100 (29.1%) patients. Collapsing (COL), cellular (CEL), and perihilar (PHI) variants were seen in 58 (16.9%), 6 (1.5%), and 3

(0.7%) patients, respectively. CEL and PHI variants were excluded from further analysis due to small patient numbers. The mean follow-up period was 36.5 ± 29.2 months. Regarding response rates of variants, patients with TIP lesions achieved remission more frequently (59.5%) than patients with NOS (41.8%) and COL (24.52%) variants ($P < 0.001$). The hazard ratio of complete response among patients with the COL variant was 0.163 [95% confidence interval (CI): 0.039-0.67] as compared to patients with NOS. The TIP variant showed a hazard ratio of 2.5 (95%CI: 1.61-3.89) for complete remission compared to the NOS variant. Overall, progressive KF was observed more frequently in patients with the COL variant, 43.4% ($P < 0.001$). Among these, 24.53% of patients required kidney replacement therapy ($P < 0.001$). The hazard ratio of doubling of serum creatinine among patients with the COL variant was 14.57 (95%CI: 1.87-113.49) as compared to patients with the TIP variant.

CONCLUSION

In conclusion, histological variants of FSGS are predictive of response to treatment with immunosuppressants and progressive KF in adults in our setup.

Key Words: Adults; Columbia classification; Focal segmental glomerulosclerosis; Histological variants; Kidney failure; Kidney failure with replacement therapy

Core Tip: Focal segmental glomerulosclerosis (FSGS) is one of the most common glomerular diseases and a leading cause of kidney failure. FSGS is a heterogeneous disorder with many causes, varying pathogenesis and clinical courses. Columbia classification identified five histological variants of FSGS. The prognostic significance of these has remained controversial. Early studies found a good correlation of the variants with clinical presentation, treatment responses, and final outcomes. However, a more recent Japanese study found no prognostic value of the variants. The present study aimed to determine the clinical significance of these variants in a large sample of the Pakistani adult FSGS population.

Citation: Jafry NH, Manan S, Rashid R, Mubarak M. Clinicopathological features and medium-term outcomes of histologic variants of primary focal segmental glomerulosclerosis in adults: A retrospective study. *World J Nephrol* 2024; 13(1): 88028
URL: https://www.wjgnet.com/2220-6124/full/v13/i1/88028.htm
DOI: https://dx.doi.org/10.5527/wjn.v13.i1.88028

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a histological pattern of glomerular injury rather than a specific diagnosis. It can occur either in a primary or idiopathic form or may be associated with various systemic diseases, including autoimmune diseases, infections, drugs, and structural kidney diseases. The key pathological finding of FSGS on light microscopy is the obliteration involving a portion (segmental) of glomerular tufts of some (focal) but not all glomeruli by increased mesangial matrix. The underlying cause of idiopathic FSGS is uncertain although a putative circulating permeability factor is supposed to play a major role in its pathogenesis[1].

FSGS is one of the leading causes of glomerular diseases, particularly those presenting with nephrotic syndrome (NS), accounting for 20 to 40% of the pathological lesions in adult patients undergoing kidney biopsy for the evaluation of idiopathic NS[2-4]. It is also one of the most common glomerular diseases leading to kidney failure (KF) and KF requiring replacement therapy (KFRT)[2].

The classification of patients with FSGS is both challenging and controversial due to the wide variety of underlying etiologies, limited understanding of the pathogenesis, and the poor correlation between morphological lesions and response to treatment and clinical outcomes. The Columbia classification of FSGS provided a novel and pragmatic approach to classify FSGS based on histological features on kidney biopsy. This classification was supposed to help clinicians in the assessment of the prognosis of the disease and its response to therapy. The classification, first proposed by D'Agati *et al*[5], in 2004, envisioned five mutually exclusive histological variants of the disease, based entirely on light microscopic (LM) features[6]. These variants include collapsing (COL), not otherwise specified (NOS), tip (TIP), perihilar (PHI), and cellular (CEL) variants[2]. Since then, many studies of these variants have been conducted worldwide and have demonstrated a correlation of the variants with distinct clinical characteristics and prognostic and therapeutic outcomes[6-12]. The response rates are generally lowest for the COL variant, intermediate for the NOS variant, and highest for the TIP variant. On the other hand, the reported rates of KFRT are highest in the COL variant, intermediate in the NOS, and lowest in the TIP variant[13-16].

Other more recent studies have found no differences among these variants with respect to treatment responses and outcomes. A recent study from Japan by Kawaguchi *et al*[17] observed that FSGS variants alone have no significant impact on kidney outcomes after five years, while proteinuria remission was predictive of improved kidney prognosis irrespective of the variant. They suggested that specific strategies and interventions to achieve proteinuria remission for

each variant should be implemented for better kidney survival.

We previously reported that whatever the histological variant of FSGS, timely treatment with immunosuppressive drugs of all patients who fulfill the criteria is very important to achieve remission, either complete or partial remission (PR). Those patients who achieved remission did not progress to KF and did not require replacement therapy in the medium-term follow-up period[2,18].

As steroids and cyclosporine (CsA)-induced remission is associated with better long-term survival, it is important to study which type of FSGS variants are more likely to respond to steroids and CsA treatment and whether such treatment affects kidney survival[2,14,17].

This study aimed to determine the relative frequency, clinicopathologic presentations, and outcomes of histological variants of FSGS in our population.

MATERIALS AND METHODS

This retrospective observational study was conducted at the Department of Nephrology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan. The study population comprised all adult patients (≥ 16 years) of either gender who were diagnosed with primary FSGS between January 1995 and December 2017. Secondary causes of FSGS were excluded. We did not analyze PHI and CEL variants in detail due to the small number of patients. Patients with missing information and irregular or erratic follow-up were also excluded.

All patients underwent ultrasound-guided percutaneous native kidney biopsies, which were processed and prepared according to standard guidelines, as described in detail in our previous studies[2,18,19]. The histological variants were diagnosed as per the criteria of the Columbia classification[5,6]. Briefly, the TIP variant was diagnosed when at least one segmental lesion involved the tip domain (outer 25% of the tuft next to the origin of the proximal tubule). It required the exclusion of COL and PHI variants. The tubular pole needs to be identified in the defining lesion. FSGS, NOS, was diagnosed when at least one glomerulus showed a segmental increase in the mesangial matrix obliterating the capillary lumina, with or without segmental glomerular capillary wall collapse but without overlying podocyte hyperplasia. It required the exclusion of PHI, CEL, TIP, and COL variants. The COL variant was diagnosed when at least one glomerulus showed segmental or global collapse and overlying podocyte hypertrophy and hyperplasia (Figure 1). The biopsies were reported by two experienced kidney pathologists and evaluated by LM, immunofluorescence, and electron microscopy. As the criteria for genetic testing in adult patients with FSGS are still unclear, genetic testing was not performed in this cohort of patients.

All patients with all variants of FSGS were treated in the same way. Briefly, unless contraindicated, all patients were treated with prednisolone, 1 mg/kg/d for the first six weeks followed by 0.75 mg/kg/d for the next six weeks. If no remission was achieved by the end of 12 wk, prednisolone was tapered over the next four weeks and stopped. If remission occurred at any time during treatment, the same dose of steroids was given for two more weeks before slow tapering. We did not employ different treatment protocols for different variants or different patients included in this study.

The steroid-resistant cases or those in which steroids were contraindicated were treated with CsA at a starting dose of 4 mg/kg/d. If a complete or PR occurred, CsA was continued for at least one year. If no response occurred by the end of two months, the use of CsA was discontinued.

Complete remission (CR) was defined as proteinuria ≤ 0.2 g/d or when the urine dipstick was negative for proteins with a stable serum creatinine concentration (< 50% increase from the baseline). PR was defined as proteinuria between 0.21-2.0 g/d with at least a 50% reduction in proteinuria from the baseline or albumin detected on dipstick (+1 to +4). Relapse was defined as proteinuria > 3 g/d after prior reduction of proteinuria to less than 2 g/d or albumin detected on dipstick (+1 to +3 or +4). Hypertension was diagnosed when patients were treated with antihypertensive drugs or with systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg. Elevated serum creatinine was defined as an increase of serum creatinine to > 1.4 mg/dL in male and > 1.2 mg/dL in female patients. KF was defined as a sustained increase of serum creatinine concentration > 50% from the baseline (at the time of kidney biopsy) or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 according to the modification of diet in renal disease equation. KFRT was defined as the need for continuous dialysis or kidney transplantation.

Data were collected by reviewing the medical record files of all selected patients. Data were collected over the period from diagnosis of primary FSGS to the last follow-up. The demographic characteristics (age, gender), BP measurements, and laboratory investigations including proteinuria, serum albumin, serum creatinine, and urine dipstick results for albumin/red blood cells on initial and last visits were noted. Drug information and side effects of steroids were obtained. The outcome of all patients regarding sustained remission, or progression to KF/KFRT, and death was noted.

Data were entered and analyzed by SPSS software 22.0 (IBM Corp., Armonk, NY, United States). Descriptive statistics were used to summarize the continuous and categorical variables. Continuous variables such as age, BP, serum creatinine, serum albumin, 24-h proteinuria, and drug dosages, are presented as mean ± SD and median ± interquartile range (IQR), as appropriate. Categorical variables, *i.e.*, gender, sustained remission, KFRT, death, CR, PR, relapse, and hypertension are reported as frequencies and percentages. Mean differences for continuous variables and proportion differences for categorical variables between groups were compared using the student's *t*-test and Chi-square or Fisher's exact tests, as appropriate. Multivariate analysis for significant factors on univariate analysis was performed using the logistic regression method, while hazard ratios for risk factors of kidney outcome were calculated using the Cox regression model. Response rates, doubling of serum creatinine, and KFRT rates were compared between histological variants using ANOVA or Kruskal Wallis, and Chi-square tests as appropriate. A *P*-value ≤ 0.05 was considered statist-

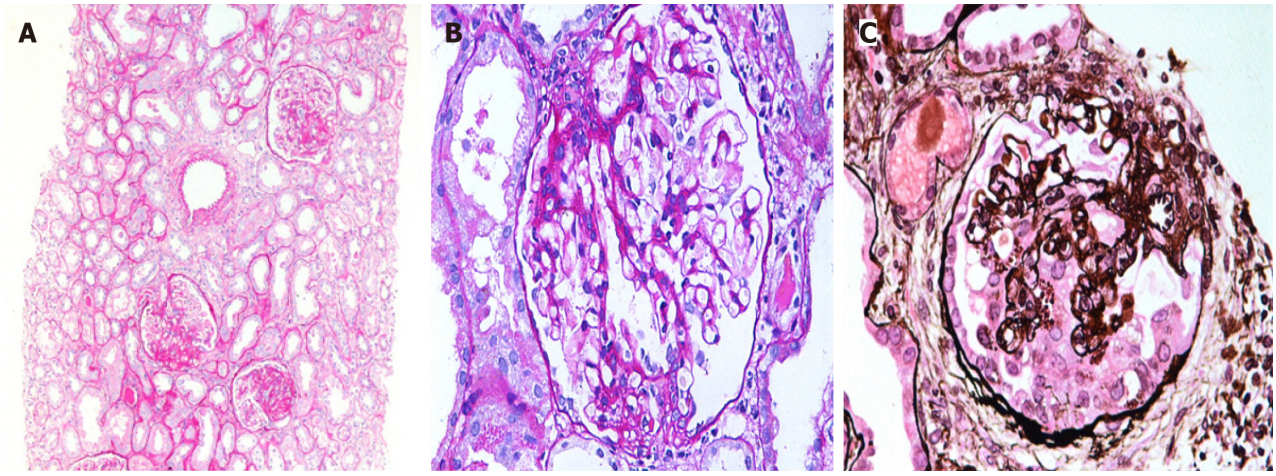

Figure 1 Histological features of common variants of focal segmental glomerulosclerosis. A: Medium-power view showing three glomeruli with segmental scars in indeterminate locations in a case of focal segmental glomerulosclerosis (FSGS), not otherwise specified. Mild patchy tubular atrophy and interstitial scarring is seen in the background [Periodic Acid-Schiff (PAS), × 200]; B: High-power view showing one glomerulus with segmental scar and adhesion formation involving the tip domain diagonally opposite the vascular pole, an example of the TIP variant (PAS, × 400); C: High-power view showing one glomerulus with segmental collapse of capillary tufts accompanied by podocyte hypertrophy and hyperplasia in a case of collapsing FSGS. Many proteinaceous droplets are also seen in the cytoplasm of podocytes (Jone's methenamine silver, × 400).

ically significant.

RESULTS

A total of 401 patients were diagnosed with primary FSGS during the study period. Among these, 352/401 (87.7%) had a designated Columbia histological variant. Among the latter, NOS was the commonest variant, found in 185 (53.9%) followed by the TIP variant in 100 (29.1%) patients. COL, CEL, and PHI variants were seen in 58 (16.9%), 6 (1.5%), and 3 (0.7%) patients, respectively. The three most common morphologic variants of FSGS (TIP, NOS, COL) comprised 343/352 (97.4%) and were included in the final analysis (Figure 2). The main demographic, clinical, and laboratory characteristics along with treatment information of these patients are shown in Table 1. There was no statistically significant difference in the mean ages of the patients with the three variants (P = 0.7). A statistically significant difference was observed in the diastolic BP where patients with the COL variant showed a higher value of 87.6 ± 14.1 mmHg compared to other histologic variants (P = 0.04). Initial proteinuria was nephrotic-range in all patients with a median (IQR) of 3774 (2216-5900) mg/24 h and there was no significant difference among the variants (P = 0.418). The initial eGFR was 83.9 (55.9-127.4) mL/min/1.73 m^2 in all patients with no significant difference among the three variants (P = 0.463). Elevated serum creatinine at presentation was found in 82 patients: Of these, 58 were males and 24 were females (P = 0.25). The mean follow-up duration in all patients was 36.5 ± 29.2 mo with no significant difference among the three variants (P = 0.114).

Of 343 patients, 302 (88%) received treatment with immunosuppressive agents combined with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) as shown in Figure 2. All patients received steroids as initial therapy as per our treatment protocol. The total duration of steroid therapy and total dose of steroids are shown in Table 1. The total dose of CsA is also shown in Table 1. The remaining patients were treated with ACE inhibitors or ARBs only due to reasons such as uncontrolled diabetes, intolerance of steroids, risk of osteoporosis, and other complications of immunosuppressive drugs.

Table 2 shows the details of pathological findings in the three morphological variants of FSGS. Upon review of the histopathological findings, a statistically significant difference was found among the three most common variants with respect to the number of glomeruli with global sclerosis (P = 0.001), number of glomeruli with segmental collapse (P = 0.05), and mild and moderate tubular atrophy (P < 0.001).

The treatment responses and clinical outcomes of all selected study subjects regarding complete and PR, or no remission, as well as progressive KF/KFRT, doubling of serum creatinine at last follow-up, final eGFR, relapse, and death of the patients are shown in Table 3. Of 302 patients, 84 (27.8%) achieved CR (Figure 2). Of these, 42 had the TIP variant, with a CR rate of 42/89 (47.2%), 40 had the NOS variant with a CR rate of 40/160 (25%), and 2 had the COL variant with a CR rate of 2/53 (3.7%) (P < 0.001). A total of 49/302 (16.2%) patients achieved PR. Among these, 11 had the TIP variant with a PR rate of 11/89 (12.4%), 27 had the NOS variant with a PR rate of 27/160 (16.8%), and 11 had the COL variant with a PR rate of 11/53 (20.8%) (P = 0.005). The highest percentage of no remission was found in patients with the COL variant at 40/53 (75.5%) followed by the NOS variant, 93/160 (58.1%) (P < 0.001) (Figure 3). The COL variant showed a marked decline in final eGFR and this was significant (P < 0.001) (Figure 4).

Among all treated patients, a doubling of serum creatinine was noted in 30 (9.9%) patients. Of these, 16/160 (10.0%) had the NOS variant, 1/89 (1.1%) had the TIP variant, and 13/53 (24.5%) had the COL variant (P < 0.001).

Table 1 Demographic, clinical, and laboratory parameters at the time of presentation of the three most common focal segmental glomerulosclerosis morphologic variants

Parameters	All patients (*n* = 343)	NOS (*n* = 185)	TIP (*n* = 100)	COL (*n* = 58)	*P* value
Age (yr), mean ± SD	29.2 ± 12.0	29.3 ± 12.4	28.6 ± 11.2	30.1 ± 12.4	0.733
Male to female ratio	2.1:1	2.0:1	2.8:1	1.4:1	0.133
Systolic BP (mmHg), mean ± SD	128.8 ± 8.0	128.9 ± 18.9	127.5 ± 16.2	130.6 ± 18.9	0.575
Diastolic BP (mmHg), mean ± SD	84.6 ± 12.6	84.8 ± 12.0	82.5 ± 12.5	87.6 ± 14.1	0.045
Initial proteinuria (mg/24 h), IQR	3774 (2216-5900)	3602.5 (2125-5890)	4250 (2535 -6530)	3900 (2218-4800)	0.418
Serum albumin (g/dL), mean ± SD	2.0 ± 1.2	2.0 ± 1.3	2.2 ± 0.9	2.1 ± 1.1	0.863
Serum creatinine (mg/dL), mean ± SD	1.1 ± 0.9	1.1 ± 0.7	1.1 ± 1.1	1.2 ± 0.7	0.830
Initial eGFR (mL/min/1.73 m^2), IQR	83.9 (55.9-127.4)	85.4 (57.8-128.3)	82.3 (59.5-125.9)	69.1 (41.9-127.3)	0.463
Elevated serum creatinine, *n* (%)	82 (23.9)	43 (52.4)	20 (24.4)	19 (23.2)	0.607
Males (> 1.4 mg/dL), *n* (%)	58 (70.7)	29 (67.4)	17 (85.0)	12 (63.2)	0.257
Females (> 1.2 mg/dL), *n* (%)	24 (29.3)	14 (32.6)	3 (15.0)	7 (36.8)	
Follow-up duration (month), mean ± SD	36.5 ± 29.2	39.1 ± 31.5	31.4 ± 24.9	37.0 ± 27.7	0.114
Total steroid dose (mg), mean ± SD	4282.1 ± 1943.2	4266.9 ± 1884.1	4366.7 ± 2067.8	4186.1 ± 1935.3	0.858
Duration of steroid treatment (wk), IQR	18 (14-23)	18 (14-23)	19 (15-23.5)	17 (13.5-20.5)	0.359
Total CsA dose (mg) mean ± SD	27118.6 ± 24904.8	30002.4 ± 26537.5	25539.4 ± 28050.2	21549.7 ± 1657.7	0.447
Duration of CsA treatment (wk), IQR	16 (6.8-46.0)	16 (8.0-54.0)	17 (5.0-69.0)	12 (4.0-28.0)	0.727

NOS: Not otherwise specified; TIP: Tip; COL: Collapsing; CsA: Cyclosporine; BP: Blood pressure; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range.

Table 2 Histopathology findings on kidney biopsies in the three most common focal segmental glomerulosclerosis morphologic variants

Histopathology	All patients (*n* = 343)	NOS (*n* = 185)	TIP (*n* = 100)	COL (*n* = 58)	*P* value
No. of glomeruli, mean ± SD	17.3 ± 8.4	16.4 ± 8.7	18.1 ± 6.8	17.3 ± 9.7	0.370
No. of glomeruli with global sclerosis, mean ± SD	2.6 ± 2.2	2.1 ± 2.3	2.0 ± 0.8	3.6 ± 2.5	0.001
No. of glomeruli with segmental collapse, mean ± SD	2.9 ± 2.7	2.4 ± 1.8	2.6 ± 2.8	13.7 ± 3.3	0.050
Tubular atrophy, mild, *n* (%)	175/201 (87.1)	91 (52.0)	49 (28.0)	35 (20.0)	< 0.001
Tubular atrophy, moderate, *n* (%)	26/201 (12.9)	9 (36.6)	1 (3.8)	16(61.5)	
Fibrointimal thickening of arteries, mild, *n* (%)	25/32 (98.1)	13 (52.0)	7 (28.0)	5 (20.0)	0.413
Fibrointimal thickening of arteries, moderate, *n* (%)	7/32 (21.9)	5 (27.8)	2 (22.2)	0 (0.0)	

NOS: Not otherwise specified; TIP: Tip; COL: Collapsing.

Regarding the development of KF, 23/53 (43.3%) patients with the COL variant developed progressive KF, 13/160 (18.1%) with the NOS variant, while none with the TIP variant progressed to KF during the mean follow-up period of 36.5 months (Figure 5). Similarly, 13/53 patients (24.5%) with the COL variant, 5/160 (3.1%) with the NOS variant, and none with the TIP variant required KFRT ($P < 0.001$). A total of four patients died, 1/53 (1.8%) with the COL variant, and 3/160 (1.8%) with the NOS variant with no significant difference among the three variants.

The final kidney and patient outcomes of the three common FSGS variants are shown in Figure 3. Patients with the TIP variant achieved remission more frequently (59.5%) than those with the NOS (41.8%), and COL (24.52%) variants ($P < 0.001$). The hazard ratio (HR) of complete response among patients with the COL variant was 0.163 (95%CI: 0.039-0.67) as compared to patients with the NOS variant. Patients with the TIP variant showed an HR of 2.50 (95%CI: 1.611-3.894) for CR compared to those with the NOS variant. Overall, progressive KF was observed more frequently in patients with the COL variant at 43.4% ($P < 0.001$). Among these, 24.53% of patients required kidney replacement therapy (KRT) ($P <$

Table 3 Responses to treatment and final clinical outcomes of focal segmental glomerulosclerosis morphologic variants in patients who received treatment, *n* (%)

Outcomes	All patients (*n* = 302)	NOS (*n* = 160)	TIP (*n* = 89)	COL (*n* = 53)	*P* value
Complete remission	84 (27.8)	40 (25.0)	42 (47.1)	2 (3.7)	< 0.001
Partial remission	49 (16.2)	27 (16.8)	11 (12.4)	11 (20.8)	0.005
No remission	169 (55.9)	93 (58.1)	36 (40.4)	40 (75.5)	< 0.001
Relapse	40 (13.2)	27 (16.9)	9 (10.1)	4 (7.5)	0.029
Final eGFR (mL/min/1.73 m^2), mean ± SD	92.1 ± 57.7	94.1 ± 59.1	110.3 ± 52.8	60.0 ± 46.9	< 0.001
Doubling of serum creatinine at last follow-up	30 (9.9)	16 (10.0)	1 (1.1)	13 (24..5)	< 0.001
Kidney failure	36 (11.19)	13 (8.1)	0 (0.0)	23 (43.3)	< 0.001
Hemodialysis	18 (5.9)	5 (3.1)	0 (0.0)	13(24.5)	< 0.001
Expired	4 (1.3)	3 (1.8)	0 (0.0)	1 (1.8)	0.429

NOS: Not otherwise specified; TIP: Tip; COL: Collapsing; eGFR: Estimated glomerular filtration rate.

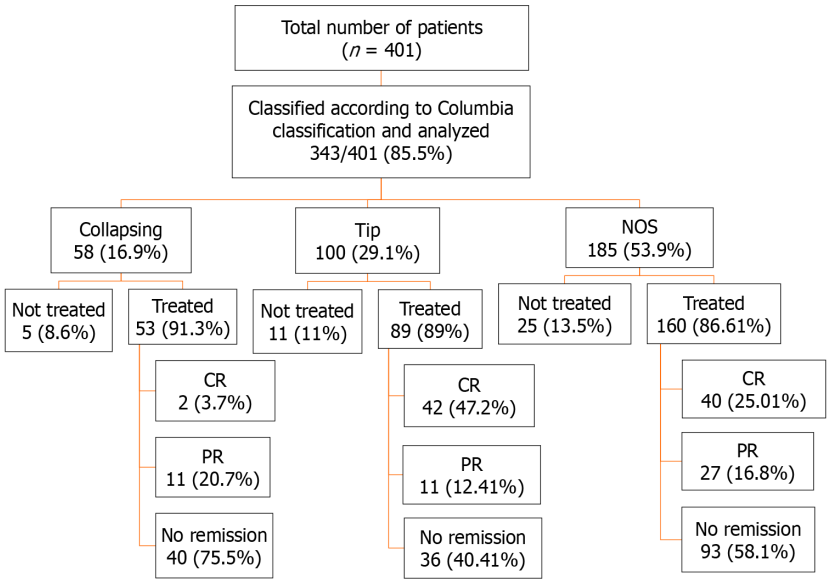

Figure 2 Flow diagram showing total number of patients and response rates of patients with the three histological variants of focal segmental glomerulosclerosis who were treated with steroids and cyclosporine. NOS: Not otherwise specified; CR: Complete remission; PR: Partial remission.

0.001). The HR of doubling of serum creatinine among patients with the COL variant was 14.577 (95%CI: 1.872-113.493) as compared to patients with the TIP variant.

DISCUSSION

This is the largest study with a cohort of 343 adult patients with biopsy-proven primary FSGS classified according to the Columbia classification from Pakistan. This study analyzed in detail the three most common morphological variants of primary FSGS, namely the NOS, TIP, and COL variants, as the numbers with the remaining two variants were very small. The vast majority of patients included in this study received treatment with steroids and CsA along with ACE inhibitors and ARBs. The total number of patients with the NOS variant was 185; of which, 160 (86.4%) patients received treatment. Likewise, there were 100 patients with the TIP variant; of which, 89 (89%) received treatment. There were 58 patients with the COL variant; of which, 53 (91.3%) patients received treatment. There is marked variation among these variants with regard to their frequency, clinical presentation, response to treatment, and prognosis in different regions of the world.

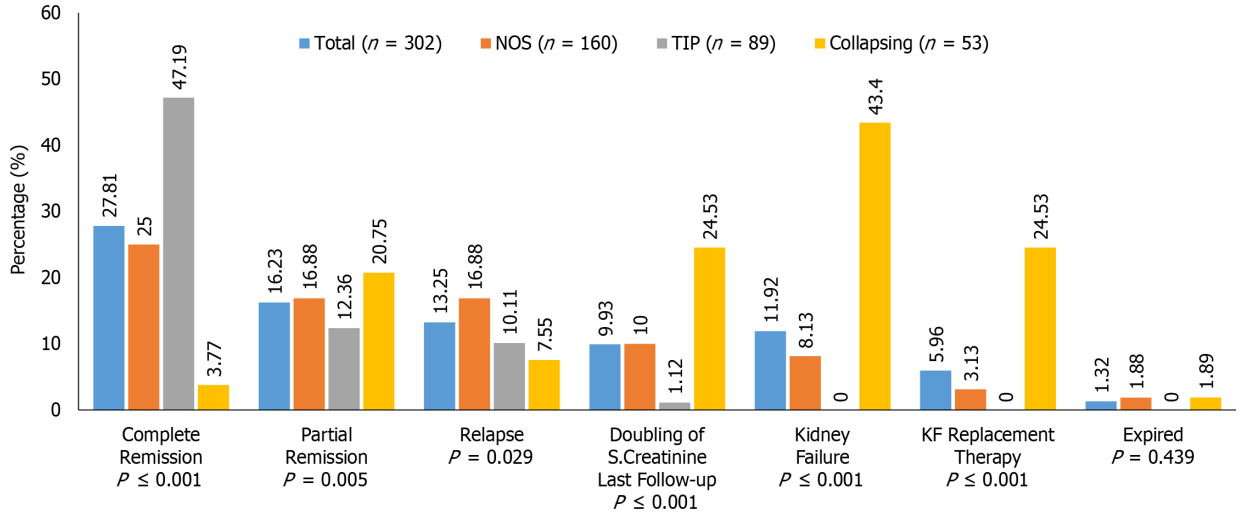

Figure 3 Treatment responses and final clinical outcomes of patients with the three most common histological variants of focal segmental glomerulosclerosis who were treated with immunosuppressive drugs (*n* = 302). NOS: Not otherwise specified; TIP: Tip; KF: Kidney failure.

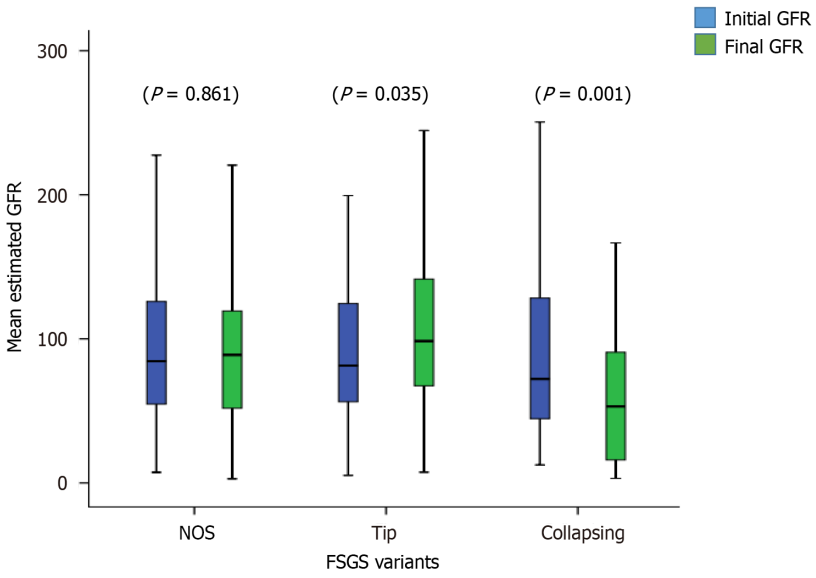

Figure 4 The means ± SDs of the initial and final estimated glomerular filtration rates of patients with the three most common histological variants of focal segmental glomerulosclerosis. FSGS: Focal segmental glomerulosclerosis; GFR: Glomerular filtration rate; NOS: Not otherwise specified.

The exact reason for the paucity of PHI and CEL variants is not clear but there may be a misclassification of the CEL variant as the TIP variant, as CEL lesions can exist within the tuft at the tubular pole as the tip location and intracapillary expansive foam cells can be observed in both variants[7].

This is one of the largest cohorts of patients with COL FSGS in the Asian population as other studies from Asia did not include such a large number of patients with this lesion. A study on a Korean population of 111 patients with primary FSGS showed 63% NOS, 18% TIP, 15% PHI, 3% CEL, and only one patient with COL FSGS[8].

In general, there is a wide diversity in the prevalence of different variants of FSGS in different regions. In a Brazilian report, NOS was the most common variant, followed by COL[7]. It was also observed that there was a substantial overlap of criteria for the NOS and PHI variants as well as for COL and CEL variants. With regard to the CEL variant, it has been claimed that it is merely a form of the COL variant, and histologically it is very difficult to differentiate between these two variants. In fact, a common pathophysiological pathway affecting cell cycle regulatory proteins has been suggested for both variants[7]. A literature review also showed that the COL variant is less common in Whites than in the Black race as compared to NOS, TIP, PHI, and CEL variants, which are not common in the Black race[6,8,12].

A literature review of published studies on the Asian population showed that in China and India, TIP, NOS, and CEL variants are more frequent morphological variants with different treatment outcomes[16,20-22]. On the contrary, we found different results in our population. Shakeel *et al*[19] studied a large cohort of 184 patients from our center. They found that the COL variant was the second most common morphological variant of FSGS in our patients. These results

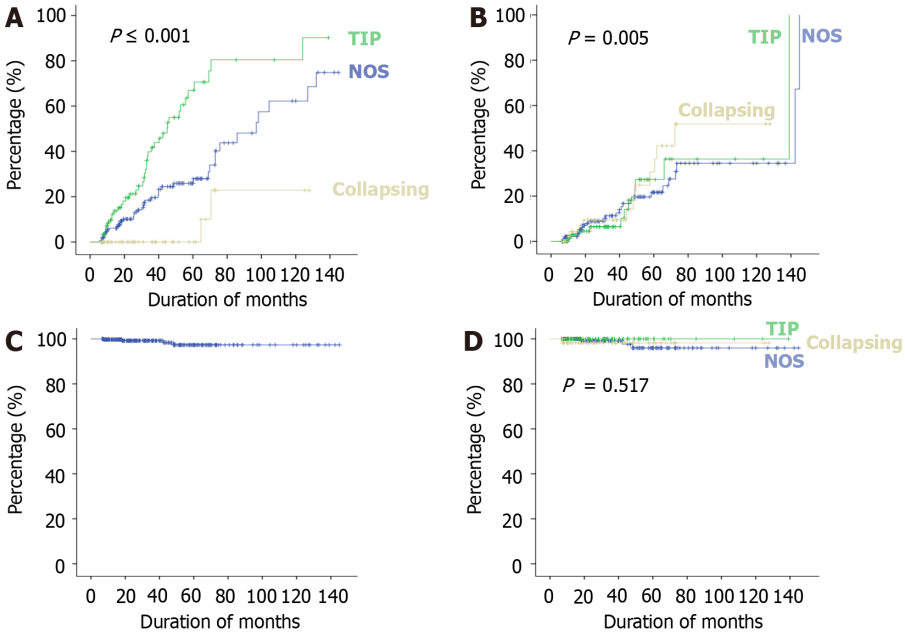

Figure 5 Treatment responses and cumulative kidney survival rates of patients with the three most common variants of focal segmental glomerulosclerosis. A: Kaplan-Meier plot of complete remission; B: Kaplan-Meier plot of partial remission; C: Kaplan-Meier plot of kidney survival (all patients); D: Kaplan-Meier plot of kidney survival by focal segmental glomerulosclerosis morphologic variants. NOS: Not otherwise specified; TIP: Tip.

were different to the Indian cohort as described previously. A more recent study from our institute evaluated the long-term outcome of adults with primary FSGS and showed a large number of patients with the COL variants after the NOS and TIP variants[2]. However, PHI and CEL variants were not common in our population as we did not find a significant number of patients with both these variants. A recent study from Japan showed a significant number of patients with PHI and CEL variants with no significant difference in outcome after treatment among different morphological variants of FSGS[17].

In our study, the majority of patients were young with an average age of 29 years, and all presented with nephrotic-range proteinuria. The mean follow-up period in our study was approximately 3 years. The primary outcome was the response to treatment and the secondary outcome was the composite outcome of the doubling of serum creatinine and KF with or without KRT. In addition, we also evaluated the improvement in eGFR as an additional outcome feature. We observed a good overall response to treatment in terms of achieving CR and PR. As in previous studies, this was highest in patients with the TIP variant, intermediate in those with the NOS variant, and lowest in patients with the COL variant. With the TIP variant, there was a > 34% increase in eGFR from the baseline after treatment which was a marked response to treatment, while in the NOS variant, eGFR increased to > 10% and in the COL variant, there was a decrease in eGFR of 13% at the end of the follow-up period. Only one patient with the TIP variant developed a doubling of serum creatinine and no patients required KFRT or expired in this group. There was a significant decline in eGFR in patients with the COL variant with only two patients out of 53 achieving CR, and 40 patients out of 53 achieved no remission. This poor outcome in those with the COL variant is similar to previous studies and observations worldwide[11,23-27]. This variant has always remained aggressive with a poor response to therapy[28-31]. However, a recent study from Japan showed almost similar outcomes for this variant compared to other variants except for the TIP variant. They proposed that this may be due to improved immunosuppressive treatment in recent years[17].

The poor outcomes in patients with the COL variant in our study are alarming in the sense that we have a large number of patients with the COL variant which ultimately can result in an increased burden of KFRT in patients in the much younger population. In those with the NOS variant, we observed that 93/160 (58.1%) patients achieved no remission. Overall, the TIP variant showed a very good response to therapy in terms of primary and secondary composite outcomes.

Two of our recent studies showed that almost half of the adults with primary FSGS achieved sustained remission with steroids and immunosuppressants, and consequently exhibited excellent short- to long-term kidney outcomes[2,18]. Almost the same results were obtained in this study in that of 302 patients, slightly less than half of the patients achieved sustained remission while 169 patients achieved no remission with a wide diversity of responses to treatment in different variants.

There are certain strengths as well as limitations in this study. The strengths include a large sample size, homogeneous race and uniform treatment protocol in all patients. Meticulous and accurate classification of morphological variants by experienced nephropathologists is also a strength of the study. We also noted some unique findings in this study. The prevalence of COL variant was quite high as compared with other regional studies. We also showed that morphological variants, if accurately classified, do have therapeutic and prognostic importance. The limitations include the single-center and retrospective nature of the study. The follow-up duration was not very long. Two variants were not analyzed due to very small numbers. Moreover, genetic testing was not performed in this cohort of patients, as currently the indications

for genetic testing in adult patients with FSGS are unclear. A pilot project to study the role of genetics in adult nephrotic patients at our center is in the pipeline and its results will be published in due course.

CONCLUSION

The histological variants of primary FSGS according to Columbia classification are associated with different clinicopathological presentations and are predictive of response to treatment and progressive KF. There was a large number of patients with the COL variant in this study, which is different to the rest of the Asian populations. These are results from a single center, and other studies are needed in order to compare the results and establish guidelines to effectively treat primary FSGS patients with different morphological variants.

ARTICLE HIGHLIGHTS

Research background

The classification of focal segmental glomerulosclerosis (FSGS) is controversial and challenging. There is still a lack of a unified and consensus-based approach to classify this disease, which will be both practical and clinically useful.

Research motivation

This study addressed the clinical utility of the morphological classification of FSGS in real-world scenarios. We aimed to investigate the therapeutic and prognostic significance of the morphological variants of FSGS in a large cohort of adult patients.

Research objectives

This study aimed to determine the relative prevalence, clinicopathologic presentations, and outcomes of the morphological variants of FSGS in a large cohort of adult patients at a single center in Pakistan.

Research methods

This retrospective study included all consecutive adults (≥ 16 years) with biopsy-proven primary FSGS from January 1995 to December 2017. Studied subjects were treated uniformly with steroids and cyclosporine. The response rates and kidney outcomes were compared between histological variants using appropriate statistical tests. Data were analyzed using SPSS version 22.0. A *P*-value ≤ 0.05 was considered statistically significant.

Research results

The not otherwise specified (NOS) variant was the most common, being found in 185 (53.9%) patients, followed by the TIP variant in 100 (29.1%) patients. Collapsing (COL), cellular, and perihilar variants were seen in 58 (16.9%), 6 (1.5%), and 3 (0.7%) patients, respectively. The response rates were highest in patients with the TIP variant and lowest in those with the COL variant. Kidney outcomes were best in patients with the TIP variant and worst in those with the COL variant. The NOS variant was intermediate.

Research conclusions

The morphological variants of FSGS are relevant and should be utilized to inform treatment and prognosis in individual patients. Combining these with other clinicopathological features to refine their predictive value needs to be investigated in future studies.

Research perspectives

A holistic approach to disease categorization needs to be developed, which is practical and clinical-friendly.

FOOTNOTES

Author contributions: Jafry NH and Mubarak M conceived and designed the study; Jafry NH, Manan S, Rashid R, and Mubarak M performed the research; all four participated in primary and final drafting; all read and approved the final manuscript; all four authors contributed significantly and equally to preparation of the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Sindh Institute of Urology and Transplantation.

Informed consent statement: All study participants or their legal guardian provided informed written consent regarding personal and medical data collection prior to study enrolment.

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

Data sharing statement: Data are available from the first author and can be shared on reasonable request.

Country/Territory of origin: Pakistan

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S-Editor: Qu XL
L-Editor: Webster JR
P-Editor: Zhao S

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World Journal of Nephrology

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

World J Nephrol 2024 March 25; 13(1): 88972

DOI: 10.5527/wjn.v13.i1.88972

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Retrospective Study

Exploring kidney biopsy findings in congenital heart diseases: Insights beyond cyanotic nephropathy

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Specialty type: Urology and nephrology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ong H, Malaysia

Received: October 18, 2023
Peer-review started: October 18, 2023
First decision: December 7, 2023
Revised: December 20, 2023
Accepted: January 15, 2024
Article in press: January 15, 2024
Published online: March 25, 2024

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Abstract

BACKGROUND

The association between congenital heart disease and chronic kidney disease is well known. Various mechanisms of kidney damage associated with congenital heart disease have been established. The etiology of kidneydisease has commonly been considered to be secondary to focal segmental glomerulosclerosis (FSGS), however, this has only been demonstrated in case reports and not in observational or clinical trials.

AIM

To identify baseline and clinical characteristics, as well as the findings in kidney biopsies of patients with congenital heart disease in our hospital.

METHODS

This is a retrospective observational study conducted at the Nephrology Department of the National Institute of Cardiology "Ignacio Chávez". All patients over 16 years old who underwent percutaneous kidney biopsy from January 2000 to January 2023 with congenital heart disease were included in the study.

RESULTS

Ten patients with congenital heart disease and kidney biopsy were found. The average age was 29.00 years ± 15.87 years with pre-biopsy proteinuria of 6193 mg/24 h ± 6165 mg/24 h. The most common congenital heart disease was Fallot's

tetralogy with 2 cases (20%) and ventricular septal defect with 2 (20%) cases. Among the 10 cases, one case of IgA nephropathy and one case of membranoproliferative glomerulonephritis associated with immune complexes were found, receiving specific treatment after histopathological diagnosis, delaying the initiation of kidney replacement therapy. Among remaining 8 cases (80%), one case of FSGS with perihilar variety was found, while the other 7 cases were non-specific FSGS.

CONCLUSION

Determining the cause of chronic kidney disease can help in delaying the need for kidney replacement therapy. In 2 out of 10 patients in our study, interventions were performed, and initiation of kidney replacement therapy was delayed. Prospective studies are needed to determine the usefulness of kidney biopsy in patients with congenital heart disease.

Key Words: Renal biopsy; Congenital heart disease; Chronic kidney disease; Focal segmental glomerulosclerosis

Core Tip: Patients with congenital heart disease often have impaired kidney function, typically due to the presence of focal segmental glomerulosclerosis (FSGS). However, in many cases, this glomerular pathology is identified only once clinically established (nephrotic proteinuria). The aim of this study is to determine the presence of FSGS under baseline conditions (without proteinuria), and therefore, it could be speculated that a preventive treatment could delay the initiation of kidney replacement therapy.

Citation: Juarez-Villa JD, Zepeda-Quiroz I, Toledo-Ramírez S, Gomez-Johnson VH, Pérez-Allende F, Garibay-Vega BR, Rodríguez Castellanos FE, Moguel-González B, Garcia-Cruz E, Lopez-Gil S. Exploring kidney biopsy findings in congenital heart diseases: Insights beyond cyanotic nephropathy. *World J Nephrol* 2024; 13(1): 88972

URL: https://www.wjgnet.com/2220-6124/full/v13/i1/88972.htm

DOI: https://dx.doi.org/10.5527/wjn.v13.i1.88972

INTRODUCTION

The association between congenital heart disease and chronic kidney disease is well known, although its prevalence is not known. Dimopoulos *et al*[1] reported that 15.8% of adults with cyanotic congenital heart disease and 8% of patients with non-cyanotic heart disease have some degree of chronic kidney disease, and Rajpal *et al*[2] reported that 1 in 6 adults with congenital heart disease have albuminuria.

These patients are subjected to various insults associated with the disease, including pathophysiological changes such as polycythemia, cyanosis, chronic hypoxia, and alterations in renal blood flow that affect glomerular hemodynamics, as well as complex surgical interventions and prolonged stays in intensive care units, all of which can cause repeated episodes of acute kidney injury[3-7].

While there have been significant advances in understanding the pathophysiology behind the decline in kidney function in these patients, glomerular alterations associated with congenital heart disease have been reported histologically since 1960[8-11]. However, over the years, there have only been a few isolated case reports and autopsy records with histopathological descriptions of glomerular changes[12].

Among the histological findings in kidney biopsies, the most common pathological features found are glomerulomegaly, mesangial hypercellularity, glomerular capillary congestion, and segmental sclerosis[13]. The most frequently observed pattern of glomerular damage is focal segmental glomerulosclerosis (FSGS), all of these changes commonly found in maladaptive glomerulopathies[14-16], as reported in a documented case by Hida *et al*[13]. Other authors propose the term "cyanotic nephropathy" to describe the maladaptive histological manifestation of hyperfiltration due to the previously mentioned risk factors[17-19].

Nowadays, there are more tools to increase the survival of patients with cyanotic congenital heart disease. However, it is important to keep in mind that these patients still have a high risk of developing cyanotic nephropathy, even after undergoing corrective cardiovascular surgery.

The objective of this study is to determine the baseline and clinical characteristics, as well as the findings in kidney biopsies of patients with congenital heart disease.

MATERIALS AND METHODS

This is a retrospective and observational study carried out at the Nephrology Department of the National Institute of Cardiology "Ignacio Chávez". All patients over 16 years old who underwent percutaneous renal biopsy from January

2000 to January 2023 with congenital heart disease were included in the study. Patients with incomplete medical records were excluded.

The kidney biopsy was performed based on the indication and consideration of the attending nephrologist for each patient. The technique was guided by real-time ultrasound, and the approach as well as the number of needles used were determined by the responsible nephrologist.

Definitions

Complications after the biopsy were classified as major or minor complications. A major complication was defined as an event that required therapeutic intervention for resolution (*e.g.*, blood transfusion, placement of a foley catheter, cystoclysis, angiography, nephrostomy, or nephrectomy). In addition, death was also considered a major complication. A minor complication, on the other hand, was defined as an event that did not require any intervention for resolution, regardless of symptoms (*e.g.*, pain on a visual analog scale greater than 5 out of 10, need for hospitalization for further monitoring).

Minor complications included macroscopic and microscopic hematuria, hematoma regardless of size, pain, arteriovenous fistula, infection, subcapsular hemorrhage, and retroperitoneal hemorrhage. All of the above-mentioned complications were elevated to major if they required any therapeutic intervention. The need for hospitalization for monitoring a complication was not included as a second complication.

As for late complications, all patients were scheduled for a follow-up consultation one month after the biopsy to evaluate the histopathological outcome. This consultation served to rule out any late complications and to ensure that patients did not visit the emergency department during this period.

The indication for kidney biopsy was a 50% increase in proteinuria and/or a ≥ 50% increase in serum creatinine compared to the previous consultation and/or active sediment defined by erythrocyturia or leucocyturia, without a clinical event justifying the deterioration of proteinuria or increase in serum creatinine.

Statistical analysis

The normal distribution of variables was evaluated using the Shapiro-Wilk test. Quantitative variables were described using means and SD or medians and interquartile ranges (IQR), depending on their distribution. Categorical variables were described using frequencies and proportions.

RESULTS

A total of 10 cases were found from January 2000 to January 2023, of which 3 (30%) patients were female. The average age was 29 years ± 15.87 years with a body mass index of 20.11 kg/m^2 ± 7.90 kg/m^2. The time from diagnosis of congenital heart disease to biopsy was 60 (39.60) months. Among the 10 patients, only 5 (50%) had a history of hypertension. Pre-biopsy proteinuria was 4843 (4079-6490) mg/24 h with a blood urea nitrogen level of 37.25 mg/dL ± 4.74 mg/dL.

Regarding ultrasonographic findings, kidney length was 9.16 centimeters ± 1.01 centimeters, 6 (60%) patients had lobulated borders, and only 2 (20%) patients had a preserved cortex to medulla ratio. In the kidney biopsy, 4 (40%) patients had insufficient samples for diagnosis; in all cases, a 16-gauge needle was used, and a transverse approach technique was employed. The number of glomeruli obtained was 13.00 ± 6.55. There were only minor complications in 3 (30%) patients, including 2 perirenal hematomas and a patient with hematuria. The rest of the baseline characteristics are presented in Tables 1 and 2.

Histopathological findings included one case of IgA nephropathy and one case of membranoproliferative glomerulonephritis due to immune complexes. Among the remaining 8 (80%) cases, one case of FSGS with perihilar variety was found, while the other 7 cases were non-specific FSGS. The findings and diagnoses of congenital heart disease are shown in Table 3.

DISCUSSION

Research on cardio-renal syndrome has made great strides in recent times; however, there is limited evidence on kidney disease in patients with congenital heart diseases. As life expectancy in this population has increased due to therapeutic advances, a higher percentage of adults living with congenital heart diseases is expected[3-19].

The mechanisms of kidney injury in these patients include chronic hypoxia, intraglomerular hemodynamic changes, neurohormonal alterations, and even cardiac surgeries for the correction of congenital defects. These mechanisms are difficult to modify and consequently result in a significant increase in the prevalence of kidney disease in these patients[3-19].

Another significant obstacle is the identification of more accurate and sensitive diagnostic tools, as well as biomarkers for kidney function in this population. The international literature recommends requesting serum creatinine and cystatin C for the estimation of glomerular filtration rate from the first contact, given the biases in isolated creatinine measurement in these patients due to the presence of sarcopenia associated with decreased physical activity. Additionally, evaluating the presence of albuminuria as a prognostic factor is recommended. However, the role of renal biopsy in these patients is a crucial point to evaluate[20-22].

Table 1 Baseline and clinical characteristics, *n* (%)

Initial variables	Results, *n* = 10
Gender (female)	3 (30)
Age (yr)	29.00 ± 15.87
Weight (kg)	54.23 ± 27.17
Height (m)	1.62 ± 0.08
Body mass index (kg/m^2)	20.11 ± 7.90
Diagnosis-biopsy time (months)	60 (39-60)
Hypertension	5 (50)
Use loop of Henle diuretics	3 (30)
Spironolactone use	2 (20)
Use of ACE inhibitors	5 (50)
Antiplatelet use	2 (20)
Warfarin use	1 (10)
Surgery prior to kidney biopsy	5 (50)
Serum creatinine (mg/dL)	1.73 ± 2.10
Blood urea nitrogen (mg/dL)	30.57 ± 29.32
Proteinuria (mg/24 h)	4843 (4079-6490)
Hemoglobin (g/L)	15.33 ± 4.45
Hematocrit (%)	48.07 ± 17.32
Platelets × 10^9/L	288.00 ± 82.00
Hematuria	0 (0)

ACE: Angiotensin-converting enzyme; BUN: Blood urea nitrogen.

The findings from previous studies suggest a clinical association between FSGS and heart disease in pediatric patients, which may be speculated to be associated with an immune mechanism responsible for the development of FSGS that can also affect the heart. An important point to note is that these studies were performed with biopsies in the pediatric population, without studying the impact of these glomerulopathies in adulthood, both in renal and cardiac prognosis. Another disadvantage is that the prevalence of other glomerulopathies other than FSGS is unknown, as they are associated with maladaptive changes, and the biopsy result is often ignored in favor of empirical treatment[23].

In our center, within the congenital heart disease department, there is a registry of 3500 patients with congenital heart disease. We do not have the exact prevalence of chronic kidney disease in this population, but unpublished information indicates an approximate 13%[24]. Our study is one of the first to describe the long-term behavior of patients with congenital heart diseases who reach adulthood and evaluate the impact of renal damage on morbidity and mortality. One of the included patients, who had ventricular septal defect as the underlying heart disease and whose biopsy reported membranoproliferative glomerulonephritis, received treatment with steroids and calcineurin inhibitors, delaying the initiation of renal replacement therapy by 3 years. Another one of our patients with ventricular septal defect who underwent successful closure of the defect had IgA nephropathy as a finding in the kidney biopsy, and received immunosuppressive treatment with steroids, delaying the initiation of kidney replacement therapy by 24 years. In both cases, these treatments would not have been given without a histopathological report justifying these interventions.

Furthermore, another important point to highlight is the prognostic information provided by these renal biopsies, as they establish a percentage of tubulointerstitial damage or fibrosis, which gives us an idea of the likelihood of recovery [25].

Another advantage of the study is the low prevalence of minor complications in only one-third of the population and the absence of major complications, indicating the safety of the kidney biopsy procedure in this patient population.

Our study has limitations such as: (1) The retrospective nature of the study and small number of cases, with only 10 patients included; and (2) the study did not focus on the medical treatment instituted to modify the decline in kidney function, as this was determined by each attending physician for each patient. However, these findings motivate the need for a prospective study with the possibility of implementing interventions that could improve the renal and cardiac prognosis in these patients.

Table 2 Baseline and clinical characteristics

Variables prior to performing the renal biopsy	Results, *n* = 10
Serum creatinine (mg/dL)	2.17 ± 1.88
Pre-biopsy BUN (mg/dL)	37.25 ± 4.74
Proteinuria prior to biopsy (mg/24 h)	6193.00 ± 6165.00
Hemoglobin (g/dL)	14.10 ± 3.76
Hematocrit (%)	43.90 ± 12.96
Hematuria	2 (20%)
Platelets × 10^9/L	281.00 ± 78.15
Skin-kidney distance (cm)	2.100 ± 0.264
Renal length (cm)	9.160 ± 1.011
Renal width (cm)	3.86 ± 0.64
Lobulated borders	6 (60%)
Ratio Cortex Medulla preserved	2 (20%)
Transverse biopsy technique	10 (100%)
Insufficient sample	4 (40%)
Number passes	1
Glomeruli	13.00 ± 6.55
Intersticial fibrosis (%)	46.67 (45.00-50.00)
Complications	3 (30%)

BUN: Blood urea nitrogen.

Table 3 Cases

Gender	Age	Type of heart disease	Diagnosis	Glomeruli	Creatinine (mg/dL)	Proteinuria (g/g/24 h)	Renal measurements (cm)	Complications
Male	17	Dextromorphism with common atrium, absence of right ventricular atrial septal defect	FSGS NOS	14	2.89	1.70	8.0 × 3.6	None
Female	23	Acianogen VSD	FSGS NOS	19	1.75	14.69	9.8 × 3.4	None
Male	47	Dextrocardia concordant atrioventricular and ventricular-arterial connection	FSGS NOS	6	1.88	1.91	9.7 × 4.6	None
Female	57	ASD	IgA nephropathy	18	1.41	3.23	8.7 × 4.2	None
Male	38	Persistent ductus arteriosus + Eisenmenger Syndrome	FSGS NOS	25	1.02	4.09	10.1 × 5.3	Haematuria
Male	33	Pulmonary atresia	FSGS NOS	6	8.25	10.89	9.4 × 4.3	Perirenal hematoma
Female	20	Infundibular VSD	GMN proliferative membrane immune complexes	11	1.98	8.25	9.9 × 4.3	None
Male	69	Ebstein Anomaly	FSGS Perihiliar	13	4.27	1.58	9.3 × 4.3	None
Male	19	Tetralogy of fallot	FSGS NOS	6	3.24	5.18	8.4 × 4.2	Perirenal hematoma
Male	41	Tetralogy of fallot	FSGS NOS	8	1.93	3.70	8.96 × 4.24	None

FSGS: Focal and segmental glomerulosclerosis; NOS: Nonspecific variety; VSD: Ventricular septal defect; ASD: Atrial septal defect.

CONCLUSION

Congenital heart disease is a growing diagnosis in the adult population and is known to be associated with chronic kidney disease. However, the etiology of chronic kidney disease in this population is not well understood. Therefore, determining the cause can help intervene in delaying the progression to kidney replacement therapy. In two out of the ten patients in our study, interventions were performed based on the renal biopsy findings, this may probably delay the initiation of renal replacement therapy.

Our study serves as an initial proposal for prospective studies to determine the importance of renal biopsy in this population. By understanding the underlying renal pathology, appropriate interventions can be implemented to improve the renal and cardiac prognosis in these patients.

ARTICLE HIGHLIGHTS

Research background

There is limited information available about the etiology of chronic kidney disease in patients with congenital heart disease today due to advanced surgeries providing an increased life expectancy, therefore it's truly important to delay the onset of kidney replacement therapy.

Research motivation

There is a growing population of patients with congenital heart disease and chronic kidney disease which is an area of opportunity to evaluate the causes of this pathology and the impact on it's treatment.

Research objectives

To determine that there may be other glomerulopathies in this population and treating them may possibly delay the onset of kidney replacement therapy.

Research methods

We conducted a retrospective analysis of information from patients with congenital heart disease who underwent kidney biopsy.

Research results

We determined that there may be other glomerulopathies in which treatment could be given. It would be appropriate to determine in a larger population if the number of other glomerulopathies different from focal segmental glomerulosclerosis (FSGS) is higher and if treatment really delays kidney replacement therapy.

Research conclusions

Chronic kidney disease in congenital heart disease is not always due to hypoxic damage that leads to FSGS.

Research perspectives

Clinical trials that can clarify who truly benefits from biopsy and enable follow-up to perform interventions that could delay renal replacement therapy.

FOOTNOTES

Author contributions: Juarez-Villa JD, Zepeda-Quiroz I, Toledo-Ramírez S, Gomez-Johnson VH, Pérez-Allende F, Garibay-Vega BR, Rodríguez Castellanos FE, Moguel-González B, Garcia-Cruz E, and Lopez-Gil S contributed to design of the study, data analysis, drafting and critical revision and editing, and final approval of the final version.

Institutional review board statement: The need for study approval was waived by the local Ethics Committee of The National Institute of Cardiology.

Informed consent statement: The need for informed consent was waived by the local Ethics Committee of The National Institute of Cardiology.

Conflict-of-interest statement: None of the authors have any conflict-of-interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: Mexico

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S-Editor: Chen YL
L-Editor: A
P-Editor: Zhao S

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World Journal of Nephrology

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

World J Nephrol 2024 March 25; 13(1): 90402

DOI: 10.5527/wjn.v13.i1.90402

ISSN 2220-6124 (online)

SYSTEMATIC REVIEWS

Prevalence and outcomes of polycystic kidney disease in African populations: A systematic review

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Specialty type: Urology and nephrology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ong H, Malaysia

Received: December 4, 2023
Peer-review started: December 4, 2023
First decision: December 28, 2023
Revised: January 3, 2024
Accepted: March 11, 2024
Article in press: March 11, 2024
Published online: March 25, 2024

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Abstract

BACKGROUND

Polycystic kidney disease (PKD) is the most common genetic cause of kidney disease. It is a progressive and irreversible condition that can lead to end-stage renal disease and many other visceral complications. Current comprehensive data on PKD patterns in Africa is lacking.

AIM

To describe the prevalence and outcomes of PKD in the African population.

METHODS

A literature search of PubMed, African journal online, and Google Scholar databases between 2000 and 2023 was performed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed to design the study. Clinical presentations and outcomes of patients were extracted from the included studies.

RESULTS

Out of 106 articles, we included 13 studies from 7 African countries. Ten of them were retrospective descriptive studies concerning 943 PKD patients with a mean age of 47.9 years. The accurate prevalence and incidence of PKD were not known but it represented the third causal nephropathy among dialysis patients. In

majority of patients, the diagnosis of the disease was often delayed. Kidney function impairment, abdominal mass, and hypertension were the leading symptoms at presentation with a pooled prevalence of 72.1% (69.1–75.1), 65.8% (62.2–69.4), and 57.4% (54.2–60.6) respectively. Hematuria and infections were the most frequent complications. Genotyping was performed in few studies that revealed a high proportion of new mutations mainly in the *PKD1* gene.

CONCLUSION

The prevalence of PKD in African populations is not clearly defined. Clinical symptoms were almost present with most patients who had kidney function impairment and abdominal mass at the diagnostic. Larger studies including genetic testing are needed to determine the burden of PKD in African populations.

Key Words: Polycystic kidney disease; Africa; Genetic disorder; Systematic review

Core Tip: Polycystic kidney disease is the most common genetic disorder affecting the kidney. The two main forms are autosomal dominant polycystic disease and autosomal recessive polycystic disease. It can lead to numerous complications with a natural progression leading to End stage kidney disease. Though the disease is well known and described in developed countries, its characteristics are still poorly understood in Africa. Indeed, as it appear in the present review, few studies regarding this disease were performed in the continent but reveal that advanced symptoms are already present in most of patients at the time of the diagnostic and the few studies with genetic testing revealed many new mutations.

Citation: Ndongo M, Nehemie LM, Coundoul B, Diouara AAM, Seck SM. Prevalence and outcomes of polycystic kidney disease in African populations: A systematic review. *World J Nephrol* 2024; 13(1): 90402
URL: https://www.wjgnet.com/2220-6124/full/v13/i1/90402.htm
DOI: https://dx.doi.org/10.5527/wjn.v13.i1.90402

INTRODUCTION

Polycystic kidney disease (PKD) is the leading hereditary cause of chronic kidney disease. Autosomal dominant PKD (ADPKD) is its most frequent type with a reported prevalence to be between 1 in 400 and 1 in 1000 Live births in the world and is typically diagnosed later in life than autosomal recessive PKD (ARPKD)[1]. The prevalence, clinical and prognosis patterns of the disease are now well-documented in high-income countries. These advances have led to new therapeutic approaches that help slowing disease progression[2]. However, in low-resource settings such as in African countries, the lack of robust data on epidemiology, clinical presentation and prognosis of PKD are scarce. Also, a later diagnosis, fewer access to healthcare and new treatments are all factors that can explain a different epidemiology. We performed this systematic review to clarify the prevalence and outcomes of PKD in the African population.

MATERIALS AND METHODS

This systematic review was conducted in October 2023 to assess the prevalence and outcomes of PKD in the African populations. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed to shape the study design[3].

A literature search of relevant articles published from January 2000 to September 2023 were performed on the online database PubMed, African journal online and google scholars. We also screened references of included articles to identify other potential studies. The keywords used for searching included: "Polycystic kidney disease" and "each of the 54 African countries name". The search was realized by using different combination of these terms.

We included: (1) Observational studies with a description of the number of PKD cases; (2) Studies that offer a description of clinical manifestations at presentation; (3) Studies published in English or French; and (4) Case reports and case series with descriptions of genetic anomalies were also included.

Studies were excluded if they presented any one or more of the following criteria: case report, case series, abstracts, commenters or letter to the editor, systematic review and meta-analysis; language other than French or English, and study with age restriction of the participant.

After eliminating duplicates, the titles and abstracts of all articles were reviewed and full texts of all articles designated for inclusion was obtained to ensure that they met the criteria for inclusion in this analysis.

For each study, we extracted the following data: study design, country, number of subjects included, demographic characteristics of patients, symptoms (hypertension, flank pain, hematuria, kidney function impairment), genetic mutation, complications, and prognosis.

Table 1 Characteristics of the different included studies

Ref.	Country	Patients	Design	Study period	Number of cases	Mean age (yr)	Gender M/F
Hajji *et al*[4], 2019	Tunisia	ADPKD	Observational descriptive	1969-2016	569	48.5	297/272
Arogundade *et al*[5], 2018	Nigeria	ADPKD	Observational descriptive	1996-2010	41	48.6 4.6	23/18
Chijioke *et al*[6], 2010	Nigeria	ADPKD	Observational descriptive	1994-2009	78	49.8 3.6	52/26
Ogiator *et al*[7], 2021	Nigeria	ADPKD	Observational descriptive	2013-2020	19	42.8 16.9	10/9
Mawufemo *et al*[8], 2018	Togo	ADPKD	Observational descriptive	2010-2017	27	51.6 16.4	10/17
Fary Ka *et al*[9], 2010	Senegal	ADPKD	Observational descriptive	1995-2005	55	47.0 5.0	31/24
Okyere *et al*[10], 2021	Ghana	ADPKD	Observational descriptive	2007-2018	82	43.8 15.7	43/39
Laleye *et al*[11], 2012	Benin	ADPKD	Observational descriptive	2000-2010	32	47.2	17/15
Abdelwahed *et al*[12], 2022	Tunisia	ADPKD	Observational descriptive	NA	19	47 18	10/9
Abdelwahed *et al*[13], 2018	Tunisia	ADPKD	Observational descriptive	NA	18	45	8/10
Seck *et al*[14], 2013	Senegal	ADPKD	Case report	NA	1	41	0/1
Sahnoun *et al*[16], 2015	Tunisia	ADPKD	Case report	NA	1	52	1/0
Nabhan *et al*[15], 2015	Egypt	ARPKD	Case report	NA	1	2.5	0/1
Total					943	47.9	502/441

ADPKD: Autosomic dominant polycystic kidney disease; ARPKD: Autosomic recessive polycystic kidney disease; NA: Not available.

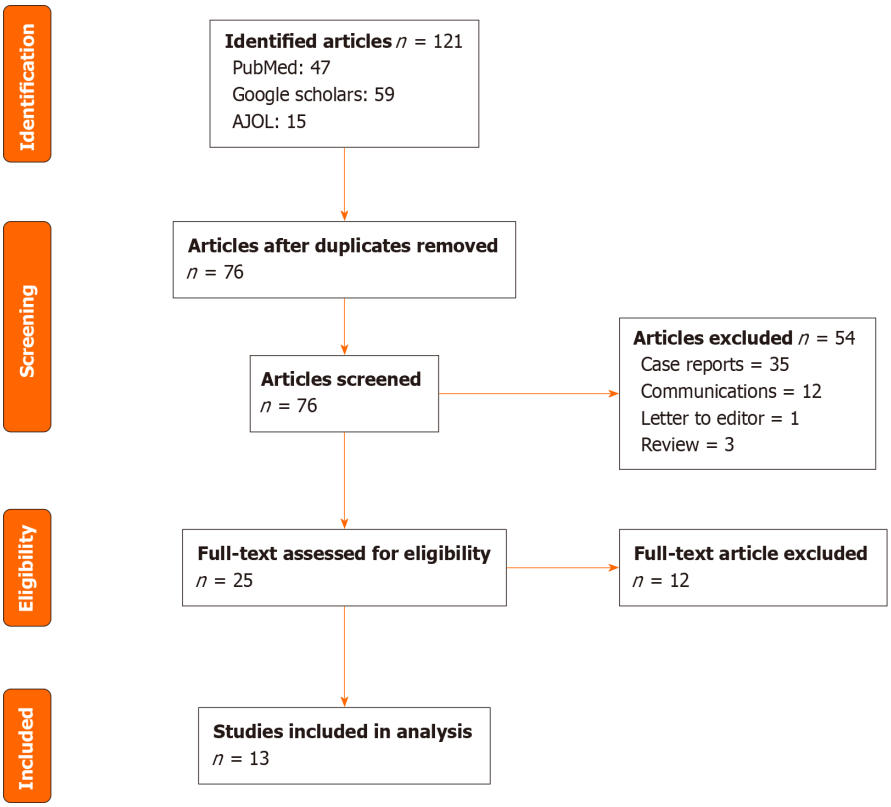

Figure 1 PRISMA flowchart of the review shape.

RESULTS

Figure 1 present the PRISMA flow diagram detailing the review shape and studies selection process. We included 13 studies from different countries as detailed in Table 1. Ten of them were retrospective observational descriptive studies[4-13] and 3 were cases reports with genetic testing performed[14-16].

Table 2 Main clinical manifestations at presentation

Ref.	HTN (%)	Pain (%)	Hematuria (%)	Abdominal mass (%)	KFI (%)	ESKD (%)
Hajji *et al*[4], 2019	58.8	51.9	24.6	66.0	74.7	23.0
Arogundade *et al*[5], 2018	87.8	68.3	36.6	82.9	100.0	19.5
Chijioke *et al*[6], 2010	26.9	14.1	NA	NA	32.0	NA
Ogiator *et al*[7], 2021	42.1	68.4	31.6	NA	63.2	15.8
Mawufemo *et al*[8], 2018	77.8	63.0	22.2	63.0	63.0	25.9
Fary Ka *et al*[9], 2010	65.4	52.7	25.4	NA	NA	NA
Okyere *et al*[10], 2021	50.0	39.0	2.4	NA	81.7	15.9
Laleye *et al*[11], 2012	59.0	62.0	46.0	43.0	72.0	NA
Abdelwahed *et al*[12], 2022	57.9	NA	26.3	NA	89.5	NA
Abdelwahed *et al*[13], 2018	72.2	NA	NA	NA	NA	NA
Pooled prevalence [95%IC]	57.4 [54.2–60.6]	49.1 [45.8–52.3]	24.0 [21.1–26.9]	65.8 [62.2–69.4]	72.1 [69.1–75.1]	21.9 [18.9–24.9]

NA: Not available; HTN: Hypertension; KFI: Kidney function impairment; ESKD: End stage kidney disease.

A total of 943 patients with PKD were collected. The mean age were 47.9 years with a sex-ratio M/F of 1.14.

Clinical symptoms were described in all the descriptive studies. Overall, kidney function impairment, abdominal mass and hypertension were the most frequent finding at presentation, present in 72.1%, 65.8% and 57.4% of patients respectively (Table 2).

Genetics testing were performed in 5 study with a cumulated total of 40 patients[12-16]. All these patients had genetic disorders with 13 novels mutation/single nucleotide polymorphism detected. The most frequently reported mew mutations were c.496 C>T, p.L166 among exon4; c.696 T>G, p.C232W among exon5; c.7290_7291delinsCTGCA among exon18 and c.12276 A>G, p.A4092 among exon45 in the *PKD1* gene (Table 3). The mutations concerned in 92.5% of cases the *PKD1* gene and in 7.5% the *PKD2* gene. In sub-Saharan Africa, seven new mutations were reported from Benin and one from a Senegal[11,14].

One case of ARPKD were reported in Egypt with a mutation (c.3367G>A, p.G1123S) in PKHD1[15].

DISCUSSION

PKD is a major public health problem that concerns all continents and ethnic groups. It is an incurable condition with a natural evolution leading to end-stage renal disease and can cause many other visceral complications. ADPKD and ARPKD are its two main types. ADPKD is commonly described in adults, whereas ARPKD is less frequent and usually presents during early childhood. ADPKD is the most frequent genetic cause of renal failure in adults, accounting for 6%–10% of end-stage renal disease cases. Its reported prevalence is similar around the globe. In the United States the reported diagnostic prevalence of ADPKD was 4.3 per 10000[17]. A large review study including 19 European countries revealed a prevalence of 3.96 per 10000[18]. However, as it appears in this review, the prevalence of PKD in Africa remains difficult to establish. Indeed, only one study from the Seychelles has reported a nationwide prevalence of 5.7 per 10000[19]. A broad range of mutations in *PKD* genes can lead to ADPKD. These disorders are widely distributed and can occur across the entire sequence of these genes, named PKD1 and PKD2. The *PKD1* gene region is larger and counts 46 exons and its mutations are responsible for around 85% of cases[20]. The PKD2 region is shorter and comprise only 15 exons with mutations causing 15% of ADPKD cases[20]. More than 1500 mutations of these two genes are indexed in ADPKD mutation databases[21]. Genotyping is usually necessary in persons with suspected PKD who do not meet the echographic criteria and/or compatible familial history. In the United Kingdom, new PKD1 mutations represented 5% of ADPKD patients[22]. Results of a few genetic tests performed in African patients found that 90% of mutations were located in the *PKD1* gene and 48.1% of them were new mutations not previously described in non-African populations. Such findings expose the need for broader genetic testing for a better PKD description in the continent. Despite similar clinical manifestations, mutations in the *PKD1* gene are associated with an earlier onset of symptoms and ESKD compared to PKD2 mutation[23]. In the literature, the reported ages at ADPKD diagnosis were 42 and 56 years, respectively for PKD1 and PKD2 patients[23]. In the present review, the mean age of patients at diagnosis was 47.9 years. In India, this age was 45.8 years[24].

Furthermore, in the majority of patients, clinical symptoms are already present at diagnosis. Hypertension, abdominal mass, flank pain, hematuria, urolithiasis, infection, and kidney function impairment were the main symptoms reported in African patients with ADPKD. The pooled proportion of ESKD was 21.9% and comparable to data from France and Canada where 22% and 25% respectively presented with ESKD at the time of diagnosis[25,26].

Table 3 Genetic analysis finding

Gene	Exon/Intron	Nucleotide change	Aminoacid change	Number of patients	Ref.
PKD 1	4	**c.496 C>T**	**p.L166**	2	[12]
	5	**c.696 T>G**	**p.C232W**	2	[12,13]
	5	**c.688 T>G**	**p.C230G**	1	[12]
	5	**c.690 C>G**	**p.C230W**	1	[12]
	7	c.1522 T>C	p.C508R	1	[12]
	8	c.1702 G>A	p.A568T	1	[12]
	9	**c.1745_1761dup**	NA	1	[11]
	15	c.4264 G>A	p.A1422T	1	[12]
	15	c.5577 T>C	p.A1859	1	[12]
	15	c.4495 C>T	p.L1499	2	[12]
	15	NA	**p.Q1651X**	1	[11]
	15	NA	**p.W1666X**	1	[11]
	15	NA	c.6575_6581del	1	[11]
	18	***c.7290_7291delinsCTGCA***	NA	2	[11,14]
	IVS22	c.8161-1 G>A	Likely silent	4	[12]
	IVS42	c.11712+28 C>T	Likely silent	1	[12]
	23	c.8679 C>G	p.S893	1	[12]
	23	c.8715 C>T	p.V2905	1	[12]
	23	c.8748 T>C	p.P2916	2	[12]
	23	**c.8522 A>G**	**p.N2841S**	1	[12]
	23	NA	**p.Q2824X**	1	[11]
	26	**c.9397+1_9397+8del**	NA	1	[11]
	28	c.9669 G>A	p.T3223	2	[12]
	30	c.3367G>A	p.G1123S	1	[15]
	31	**c.10165 G>C**	**p.E3389Gln**	1	[12]
	44	c.12133 A>G	p.I4045V	1	[12]
	45	**c.12276 A>G**	**p.A4092**	2	[12,16]
PKD 2	1	c.568 G>A	p.A190T	2	[12]
	1	c.83 G>C	p.A28P	2	[12]
	IVS1	c.596-16 C>T	Likely silent	1	[12]
PKHD1		c.3367G>A	p.G1123S	1	[15]

In bold: New mutation found. NA: Not available.

In the United States, ADPKD is the fourth leading cause of ESKD requiring dialysis and transplantation[27].

Less common than ADPKD, ARPKD is a childhood-onset disease with symptoms that can appear in perinatal. It is linked to the mutations *PKHD1* gene with an estimated prevalence of 1 in 20000 live births in Caucasians[28]. In Africa, its prevalence is still not known, one case was reported in an Egyptian child. A mean age at diagnosis of 4 years was reported with around 60% of patients with ESKD before adulthood[29].

CONCLUSION

PKD represents the most frequent genetic disorder. ADPKD is by far more frequent than ARPKD. In Africa, little data on the prevalence, clinical presentation, and evolution of this disease are available, and genetic testing is even more lacking.

Clinical symptoms were almost present with most patients who had kidney function impairment and abdominal mass at the diagnosis. As shown in this review, many new mutations were found in the *PKD1* gene. More large-scale studies are needed to describe the patterns of these diseases.

ARTICLE HIGHLIGHTS

Research background

Polycystic kidney disease is known as the most common genetic cause of chronic kidney disease. Its natural evolution lead to end-stage kidney disease. However, unlike developed countries, clinical and prognosis outcomes data of the disease are lacking in African population.

Research motivation

Mapping the data of polycystosis in African population and emphasize the gap between data from international literature and those available in our specific population and outline points for further studies.

Research objectives

Describe the prevalence, clinical, and genetic aspects of polycystic kidney disease in an African population.

Research methods

A literature review and meta-analysis of available data were performed from January 2000 to September 2023 to identify reported data of prevalence, clinical manifestation, and genetics anomalies of patients with polycystic kidney disease in the continent.

Research results

A total of 943 patients with polycystic kidney disease were reported in the period of research but the real prevalence of the disease is not known in the continent. Most patients present with symptoms at diagnosis mainly kidney function impairment and abdominal mass. Nevertheless, the mean age at diagnosis is similar to the literature data. Genetic testing was not frequent, however, they showed a high proportion of new mutations.

Research conclusions

Most African patients with polycystic kidney disease present with severe symptoms and complications at diagnosis. A high proportion of new mutations were reported in this population particularly in the *PKD1* gene.

Research perspectives

Further researches are needed to better assess the real prevalence of PKD and the spectrum of mutations in the continent.

FOOTNOTES

Author contributions: Seck SM and Ndongo M designed the study and performed the research; Seck SM and Ndongo M analyzed the data and wrote the manuscript; Ndongo M, Nehemie LM, Coundoul B, Diouara AAM and Seck SM edited and reviewed the manuscript; the manuscript has been read and approved by all authors.

Conflict-of-interest statement: All authors have no conflict of interest to disclose for this article.

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

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhao YQ

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