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Case Report

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Editorial

Sepsis and Acute Kidney Injury (AKI): Which is More Important, Sepsis Biomarkers or AKI Biomarkers?

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Sepsis and acute kidney injury (AKI) are two major global health problems and are strongly associated with poor outcomes. Although often used interchangeably in clinical practice, there are conditions associated with sepsis and AKI that are fundamentally different in their underlying pathophysiology. Sepsis-associated AKI (SA-AKI), which is AKI that occurs concurrently with or within 7 days of the diagnosis of sepsis[1], and sepsis-induced AKI (SI-AKI), which is a sub-phenotype of SA-AKI in which sepsis serves as the primary and dominant trigger for kidney injury.[2] In SA-AKI, sepsis is not always the sole direct cause of AKI. The occurrence of AKI can be exacerbated by the use of nephrotoxic drugs during treatment or other comorbid medical conditions. On the other hand, in SI-AKI, AKI occurs directly due to mechanisms triggered by sepsis, such as cytokine storm, impaired renal microcirculation, and oxidative stress in renal tubular cells.

Which biomarker is more important to evaluate in critically ill patients: biomarkers for sepsis or biomarkers for AKI?

In a clinical context, evaluating sepsis biomarkers or AKI biomarkers is equally important, but they have different roles depending on the purpose. Whether the evaluation is performed to detect the cause of AKI or to detect the presence or absence of kidney disorders. However, sepsis and AKI can also occur simultaneously. Clearly, the prognosis of both SA-AKI and SI-AKI is worse than that of sepsis and AKI separately.[3] Patients with AKI due to sepsis have worse outcomes than patients with AKI due to other causes (i.e., non-septic AKI). Conversely, patients with sepsis and AKI who experience improvements in urine output, serum urea levels, and creatinine levels 48 hours after hospital admission have lower mortality rates than patients with the opposite conditions.[4] Therefore, rapid and appropriate intervention will result in good outcomes. Therefore, early detection of SA-AKI and SI-AKI is crucial so that preventive measures and early treatment can be initiated promptly. A major problem to date is the lack of tools to help diagnose sepsis and AKI early and accurately.

Sepsis biomarker evaluation aims to confirm the presence of bacterial infection and determine how aggressive antibiotic therapy should be administered. Therefore, the primary priority is to identify and manage sepsis as early as possible to prevent organ damage and/or progression. Meanwhile, AKI biomarker evaluation aims to detect kidney impairment early, even at subclinical stages, and monitor the severity and risk of permanent kidney disease. Recognizing kidney stress increases physicians'

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caution in prescribing medications or managing fluids to avoid worsening kidney conditions.

Use of AKI and Sepsis Biomarkers in Critically Ill Patients

The role of biomarkers in identifying sepsis and AKI is crucial for the diagnosis, treatment, and prognosis of these conditions. However, to date, no single biomarker has demonstrated sufficient specificity or discriminatory value to be used decisively and reliably in the diagnosis and/or prognosis of these disorders.[5] There is no ideal sepsis screening tool that achieves both high sensitivity and specificity.[6] Sepsis remains a clinical diagnosis and should neither be confirmed nor excluded on the basis of a single biomarker or diagnostic test alone. On the other hand, sepsis treatment is highly time-dependent.[7] Patients with untreated sepsis or early sepsis are at higher risk of developing SI-AKI.[8] Similarly, in patients with AKI, early diagnosis remains challenging. Creatinine has many limitations, while early biomarkers are not yet widely accessible in clinical practice. Therefore, there is a need for early, easily accessible biomarkers to diagnose structural damage before functional injury occurs. This early identification will facilitate the application of targeted therapeutic interventions, with the potential to alter the natural course of the disease.

To date, there is no 100% specific biomarker for SA-AKI. What exists are AKI biomarkers that perform better in the context of sepsis. This is because SA-AKI is mediated through multiple pathways, including systemic and renal inflammation, complement activation, Renin-Angiotensin-Aldosterone System (RAAS) dysregulation, mitochondrial dysfunction, microcirculatory dysfunction, and macrocirculatory disturbances.[1]

Proenkephalin (PENK) is a newer glomerular filtration biomarker that is exclusively filtered in the glomerulus. PENK is a highly reliable indicator of glomerular filtration injury compared to creatinine. PENK is 48 hours earlier than serum creatinine in detecting severe AKI.[8] PENK is not a sepsis biomarker, but its performance appears to be superior in patients in the setting of sepsis. In this issue of InaKidney, Wahyudi et al. found that serum PENK levels ≥82.6 pmol/L have high accuracy in the early detection of AKI in sepsis.[9] In addition to early diagnosis, serum PENK levels can also determine the severity of AKI and appear to correlate strongly with GFR.[10]

It can be concluded that identifying sepsis biomarkers or AKI biomarkers in critically ill patients is equally important. However, if one must choose which to evaluate first, sepsis biomarkers appear to be the priority in critical care because they determine life-saving interventions. However, regular monitoring of AKI biomarkers is crucial in determining whether a patient will recover fully or end up with chronic kidney disease. The consensus report of the 28th Acute Disease Quality Initiative workgroup recommends using sepsis biomarkers alongside biomarkers of functional and tubular injury to improve prognosis in early or late SA-AKI.[1] Therefore, the best approach in AKI in the setting of sepsis is to use a combination of biomarkers, for example, PENK (biomarker of functional injury) and NGAL (biomarker of tubular injury). A thorough understanding of the underlying pathophysiology and the use of appropriate biomarkers can facilitate early diagnosis and potentially improve patient outcomes through targeted therapy.

Declarations

Competing interest

The author declares no conflict of interest.

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Original Article

Characteristic of Patients Undergoing Initiation of Emergency Hemodialysis at Ngoerah Hospital Denpasar in 2023

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ABSTRACT

Background: Initiation of emergency hemodialysis is associated with higher morbidity and mortality compared to planned hemodialysis. Identifying the characteristics of patients undergoing emergency hemodialysis is essential to improving clinical outcomes.
Objective: This study aimed to describe the clinical characteristics of patients who initiated emergency hemodialysis at Ngoerah Hospital in Denpasar in 2023.
Methods: This cross-sectional descriptive study used secondary data obtained from the patient registry. Total sampling was used to include all patients who initiated emergency hemodialysis at Ngoerah Hospital between January 1 and March 31, 2023. Data were analyzed descriptively.
Results: A total of 70 patients were included. The mean age was 54.54 ± 14.6 years, and 52.3% were male. The most common etiology of CKD was obstructive nephropathy (32.8%), followed by diabetic kidney disease (21.4%). Major comorbidities included heart disease (35.7%), malignancy (25.8%), and diabetes mellitus (21.4%). The most frequent indications for emergency hemodialysis were metabolic acidosis (71.8%). Temporary jugular vein central venous dialysis catheters were the most commonly used vascular access (67.6%). Only 21.1% of patients had received pre-dialytic monitoring. The median estimated glomerular filtration rate (eGFR) was 5.69 mL/min/1.73 m^2, the median serum creatinine was 8.47 mg/dL, and the median serum potassium level was 5.6 mEq/L.
Conclusion: Patients initiating emergency hemodialysis at Ngoerah Hospital demonstrated diverse clinical characteristics. The high prevalence of metabolic acidosis along with low rates of pre-dialytic monitoring, highlights the need for improved early detection and management of CKD to reduce emergency hemodialysis initiation.
Keywords: Emergency hemodialysis, patient characteristics, chronic kidney disease, Ngoerah Hospital Denpasar.

Introduction

Chronic kidney disease (CKD) represents a global health problem, with its prevalence steadily increasing every year. Chronic kidney disease is defined as kidney damage that occurs for more than 3 months, in the form of structural or functional abnormalities, with or without a decrease in glomerular filtration rate or a glomerular filtration rate <60ml/minute/1.73m2 for 3 months with or without kidney damage. CKD is a condition of progressive loss of kidney function, which ultimately results in the need for kidney replacement therapy, such as dialysis or kidney transplantation.[1]

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Chronic kidney disease affects approximately 800 million people worldwide. The prevalence of CKD is 8.6% and 9.6% in men and women in high-income countries, and 10.6% and 12.5% in men and women in low- and middle-income countries.[2] A meta-analysis of 100 studies involving 6,908,440 patients reported a global prevalence of CKD stages 1–5 is 13.4% and 10.6% for CKD stages 3–5. The prevalence of CKD based on stage is 3.5% (stage 1), 3.9% (stage 2), 7.6% (stage 3), 0.4% (stage 4), and 0.1% (stage 5).[3] In Indonesia, based on 2018 Riskesdas data, the prevalence of CKD reached 3.8% of the population.[4] Chronic kidney disease has emerged as one of the main causes of death throughout the world, and is one of the non-communicable diseases that has shown an increase in mortality during the last 2 decades.[2]

Risk factors for CKD include old age, long-term exposure to nephrotoxins (non-steroidal anti-inflammatory drugs [NSAIDs], antibiotic therapy such as gentamicin), chemotherapy, history of nephrolithiasis or recurrent urinary tract infections, the presence of comorbidities (diabetes, hypertension, autoimmune diseases, chronic infections), family history of kidney disease, and genetics.[5]

The early stages of CKD are generally asymptomatic, and symptoms usually appear in stages 4 or 5. Some common symptoms and signs in the advanced stages of CKD include nausea, loss of appetite, vomiting, weight loss, weakness, sleep disturbances, oliguria, decreased consciousness, muscle cramps, leg swelling, pruritus, and shortness of breath due to pulmonary edema. On physical examination, signs are often found in the form of skin pigmentation, scratch marks due to pruritus, and uremic frost.[6] The diagnosis of CKD is made based on clinical conditions, time, and laboratory examination, most often by estimating eGFR as a marker of filtration, such as serum creatinine or by looking at the presence of albumin in urine.[5,6] In the end-stage of CKD, patients require renal replacement therapy, with hemodialysis being the most commonly used modality. However, not all patients can start hemodialysis in a planned manner. In many cases, patients must undergo emergency initiation of hemodialysis. Studies show that only around 10.5% of end-stage renal disease (ESRD) patients have arteriovenous fistula (AVF) access at the time of hemodialysis initiation.[7]

Emergency hemodialysis is a hemodialysis procedure that is carried out suddenly in patients with life-threatening clinical conditions, such as severe uremia, hyperkalemia, fluid overload, or uncontrolled metabolic acidosis. Emergency hemodialysis initiation is often associated with an increased risk of morbidity, mortality, and more expensive medical costs compared to planned hemodialysis initiation. Therefore, understanding the characteristics of patients undergoing emergency hemodialysis is essential to improve patient management and clinical outcomes. Previous studies showed that acute kidney injury (AKI) is the leading contributor to emergency hemodialysis initiation, followed by stroke, diabetes, and heart failure. To avoid the need for emergency initiation of hemodialysis, patients with end-stage renal disease (ESRD) should be referred to a nephrologist early. In addition, ESRD patients with a clinical history of AKI, stroke, diabetes, or heart failure should be carefully observed and given pre-planned initiation of dialysis.[8]

Identification of patient characteristics encompasses various aspects, such as demographics, etiology of kidney disease, indications for hemodialysis, comorbidities, and pre-dialytic monitoring. A better understanding of these characteristics may help in the development of more effective prevention, early detection, and management strategies to reduce the incidence of emergency hemodialysis and improve patient clinical outcomes.[9]

Ngoerah Hospital in Denpasar, one of the main referral centers in Bali, handles a large number of hemodialysis cases, including emergency cases. However, specific data on the characteristics of patients initiating emergency hemodialysis at this hospital remain limited. This study aims to fill this knowledge gap by analyzing the characteristics of patients undergoing

emergency hemodialysis initiation at Ngoerah Hospital, Denpasar, during the period 1 January - 31 March 2023.

Methods

The research method used is a cross-sectional descriptive study based on secondary data from the patient register. Subjects were all patients who initiated emergency hemodialysis in the hemodialysis ward at Ngoerah Hospital, Denpasar, from January 1 to March 31, 2023. This study used a total sampling method, in which all patients who met the subject selection criteria were included. The inclusion criteria used were patients who were undergoing emergency hemodialysis initiation who had complete register data (age, gender, ethnicity, etiology, comorbidities, emergency HD indications, vascular access, pre-dialytic monitoring, kidney function, and electrolytes) in the Hemodialysis ward at Ngoerah Denpasar Hospital from January 1 to March 31, 2023. Exclusion criteria were registered data outside Ngoerah Denpasar Hospital or incomplete register data. The sample size comprised all cases that met the inclusion and exclusion criteria, namely 70 samples. Data analysis was carried out using descriptive analysis. Data are presented in a frequency distribution table.

Results

A total of 70 patients who initiated emergency hemodialysis and met the inclusion and exclusion criteria were included in this study. This research was conducted to examine the characteristics of all patients who underwent emergency initiation of hemodialysis at Ngoerah Hospital from 1 January to 31 March 2023. Data on patient characteristics are presented in Table 1.

Table 1. Patients Characteristic

	n (%) **(n = 70)**
Age (Years), mean ± SD	54,54 ± 14,6
Gender, n (%)	
Male	37 (52,3)
Female	33 (47,1)
Ethnic, n (%)	
Balinese	48 (68.5)
Javanese	17 (24,2)
West Nusa Tenggara	2 (2,8)
East Nusa Tenggara	2 (2,8)
Armenia	1 (1,4)
Etiology, n (%)	
Obstructive Nephropathy	23 (32.8)
Diabetic kidney disease	15 (21.4)
Nephrosclerosis	7 (10.0)
Contrast-induced nephropathy	3 (4,3)
Chronic Pyelonephritis	4 (5.7)
Lupus nephritis	2 (2.8)
Diabetic kidney disease and Nephrosclerosis	3 (4.3)
Others	12 (17.1)
Unknown	3 (4.3)

Comorbidities, n (%)	
Heart disease	25 (35.7)
Malignancy	18 (25.8)
Diabetes mellitus	15 (21,4)
Hypertension	7 (10.0)
Pneumonia	5 (7.1)
Sepsis	9 (12.9)
Others	17 (24.3)
Indication, n (%)	
Anuria	7 (9,9)
Metabolic Acidosis	51 (71,8)
Doubling Creatinine	6 (8,5)
Pulmonary Edema	13 (18,3)
Hyperkalemia	39 (54,9)
Anemia, n (%)	
Yes	42 (60.0)
No	28 (40,0)
Vascular Access, n (%)	
Temporary femoral vein CDL	21 (30.0)
Temporary jugular vein CDL	46 (65.8)
Tunneled jugular vein CDL	3 (4,2)
Pre-dialytic monitoring, n (%)	
Yes	15 (21,1)
No	55 (78,9)
eLFG, median (min-max)	5,69 (1,13-36,23)
Creatinin, median (min-max)	8,47 (1,71-37,70)
Potassium, median (min-max)	5,6 (1,3-8,98)

* *CDL: Catheter Double Lumen*

The average patient age was 54.54 years with a standard deviation of 14.6 years. Gender distribution showed a slight male predominance, with 37 patients (52.3%) male and 33 patients (47.1%) female. The majority of patients were Balinese, at 48 (68.5%), followed by Javanese, at 17 (23.9%). There were also 2 patients each from West Nusa Tenggara and East Nusa Tenggara Timur (2.8%), and 1 patient (1.4%) from Armenia. The most common etiology of CKD is obstructive nephropathy (32.8%), followed by diabetic kidney disease in second place (21.4), and then nephrosclerosis (10%). Other etiologies that occur in small numbers include contrast-induced nephropathy, chronic pyelonephritis, lupus nephritis, a combination of diabetic kidney disease and nephrosclerosis, and others. There was also an unknown etiology (4.3%). In terms of comorbidities, 25 patients (35.7%) had heart disease, 18 patients (25.8%) had malignancy, and 15 patients (21.4%) had diabetes mellitus. Hypertension was found in 7 patients (10%), pneumonia in 5 patients (7.1%), sepsis in 9 patients (12.9%), and others in small numbers, if accumulated at (24.3%).

The main indications for emergency hemodialysis were varied, with metabolic acidosis being the most common (51 patients, 71.8%), followed by hyperkalemia (39 patients, 54.9%), pulmonary edema (13 patients, 18.3%), anuria (7 patients, 9.9%), and doubling creatinine (6 patients, 8.5%). Anemia was found in 42 patients (60%). For vascular access, the majority of patients used a temporary jugular vein catheter double lumen (CDL) (46 patients, 65.8%), followed by a temporary femoral vein CDL (21 patients, 30%), and a tunneled jugular vein CDL (3 patients, 4.2%). None of them had AVF for hemodialysis access. Only 15 patients (21.1%) received pre-dialytic monitoring, while 55 patients (78.9%) did not. The median patient eLFG value was 5.69 with a range of 1.13-36.23. Median serum creatinine was 8.47 with a range of 1.71-37.70, and median potassium was 5.6 with a range of 1.3-8.98.

Discussion

Age is an important factor in the characteristics of emergency hemodialysis patients. Studies show that patients initiating emergency hemodialysis tend to be older than those undergoing planned hemodialysis. This can be associated with an increased risk of comorbidities and decreased kidney function with increasing age.[8,10] The results of this study show that the average age of patients undergoing emergency hemodialysis is 54.54 ± 14.6 years. In a study in San Francisco, the mean age of patients undergoing emergency hemodialysis initiation was 45.9 ± 14.5 years and was not significantly different from the age of patients undergoing standard hemodialysis initiation.[11] In a study in Japan of 151 patients undergoing emergency hemodialysis initiation, the average age of patients was 65.7 ± 14.7 years, with 16.6% of patients aged over 80 years.[8] In a Korean study of 146 patients undergoing emergency hemodialysis initiation, 54 patients were predominantly aged 35-65 years (7%).[12] In a study in Taiwan from 2010-2017, patients undergoing emergency hemodialysis initiation were dominated by patients aged >75 years as much as 40%.[10]

Gender also plays a role in the characteristics of emergency hemodialysis initiation patients. Research shows that men have a higher tendency to undergo emergency hemodialysis initiation than women. Factors such as differences in lifestyle, diet, and smoking habits are hypothesized to contribute to this difference.[8] In this study, patients undergoing emergency hemodialysis initiation were predominantly male, 52.3%. This is similar to a study in Taiwan, which reported that 58% of patients initiating emergency hemodialysis were male, and to a study in Korea, which reported that 59.6% were male.[10,12] Studies in the United States also showed that 55.6% of men initiated emergency hemodialysis.[11] In a study in Japan, 70.2% of patients undergoing emergency hemodialysis initiation were men.

Comorbidities are another important characteristic of emergency hemodialysis patients. Heart disease, malignancies, diabetes mellitus, and hypertension are often found in patients undergoing emergency hemodialysis. These comorbidities can worsen the patient's condition and increase the risk of complications during hemodialysis procedures.[12] In this study, the etiology of kidney disease was mostly caused by obstructive nephropathy, which was dominated by cervical cancer in 11.2% of patients. In Korea, the most common comorbidity was hypertension at 63.9%, followed by CKD at 23.9% and HIV infection at 8.2%.[12] In the United States, as many as 50.3% experienced DM, and 12.4 % had a history of hypertension.[11] Study in Japan, as many as 37.7% had DM, 88.1% had hypertension, 41.7% had heart disease, 13.9% had stroke, 17.9% had cancer, and 13 .2% experienced acute kidney injury.[8]

The most common indication for emergency hemodialysis in this study was metabolic acidosis (71.8%), followed by hyperkalemia (54.9%), pulmonary edema (18.3%), anuria (9.9%), and doubling of creatinine (8.5%). In a similar study in Korea, the main indications for initiating emergency hemodialysis were encephalopathy (33.5%), severe uremia (28%), acute pulmonary edema (19.8%), persistent anuria (11.6%), and hyperkalemia (5, 4%).[12] In a Japanese study, indications for initiation of emergency hemodialysis were heart failure (n = 20), uremia (n = 18), AKI or Rapid progressive Glomerulonephritis (RPGN) (n = 11), hyperkalemia and/or acidosis (n = 3), and others (n = 19).[8]

In this study, vascular access for hemodialysis was dominated by temporary jugular vein catheter double lumen (67.6%), followed by temporary femoral vein CDL (28.2%), and last tunneled jugular vein CDL (4.2%). In a study in Korea, vascular access was a catheter in 97.2% (femoral site in 53.4% and jugular in 43.8%) and an arteriovenous fistula in 2.7%.[12] In emergency situations, a non-tunneled central venous catheter (CVC) is the main choice because it can be installed quickly and used immediately. Common insertion sites include the internal jugular, subclavian, or femoral veins, with the internal jugular vein often the first choice due to lower complication risk and patient comfort. Although CVCs allow immediate vascular access, their use is associated with risks such as infection, thrombosis, and catheter dysfunction. Therefore, plans to transition to a more optimal long-term vascular access, such as an arteriovenous fistula or graft, should be considered as soon as the patient's condition has stabilized. Appropriate selection and management of vascular access at the initiation of emergency hemodialysis is not only crucial for the success of the emergency procedure, but also has a significant impact on patient morbidity and mortality.[13]

A total of 78.9% of patients in this study did not undergo pre-dialytic monitoring. Studies in Taiwan showed that in 2010, as many as 75% of emergency dialysis patients did not undergo pre-dialytic monitoring, but this had decreased to 59% by 2017.[10] Pre-dialytic monitoring plays a crucial role in preventing the initiation of hemodialysis. Close, regular monitoring can help identify early changes in kidney function, allowing time for intervention before the patient's condition worsens to the point of requiring emergency hemodialysis. The pre-dialytic monitoring program includes routine checks of kidney function, blood pressure management, blood sugar control in patients with diabetes, monitoring of nutritional status, and evaluation of electrolyte balance. In addition, patients are educated about healthy lifestyles, adherence to treatment, and recognition of symptoms of worsening kidney function. By implementing pre-dialytic monitoring strategies, medical teams can slow the progression of CKD, reduce the risk of acute complications, and enable more controlled planning for dialysis initiation. This not only increases the patient's physical and psychological readiness to initiate renal replacement therapy but also reduces the burden on the health system by reducing the incidence of emergency hemodialysis, which often requires more resources. Therefore, implementing a pre-dialytic monitoring program is one strategy to

prevent the initiation of emergency hemodialysis and improving the quality of care for CKD patients.[14]

This research has several clinical implications for the management of patients undergoing initiation of emergency hemodialysis. First, a better understanding of patient characteristics can help medical teams identify risk factors and perform more accurate risk stratification. This can lead to increased awareness and readiness among the medical team to handle cases that may require emergency hemodialysis. Second, identifying patterns of comorbidities among emergency hemodialysis patients can help develop more comprehensive and integrated treatment protocols that take into account the complexity of the patient's condition. Third, understanding patient demographic characteristics can help in planning hemodialysis unit resources and capacity, especially to accommodate emergency hemodialysis needs.

Conclusion

The characteristics of patients undergoing initiation of emergency hemodialysis at Ngoerah Hospital, Denpasar, show variations in demographic and clinical aspects. The high percentage of metabolic acidosis and hyperkalemia as indications, as well as the low rate of pre-dialytic monitoring, indicate the need for improvements in early detection and management of CKD patients to reduce the need for emergency hemodialysis.

Limitations of the Study

This study has several weaknesses that warrant consideration. First, the use of a cross-sectional descriptive study design limits the ability to draw causal conclusions or analyze changes in patient characteristics over time. Second, secondary data sources from patient registers can introduce bias regarding the completeness and accuracy of the data, especially if there are inconsistencies in recording or input errors. Third, the relatively short data collection period (3 months) may not be representative enough to comprehensively describe patient characteristics, especially if there are seasonal variations in emergency hemodialysis cases. Fourth, the study was conducted at only one type A hospital, limiting the generalizability of the findings to broader populations or other hospital settings. Fifth, the absence of a comparison group (e.g., elective hemodialysis patients) limits the ability to identify unique characteristics of emergency hemodialysis patients. Lastly, data analysis limited to descriptive methods may not reveal more complex relationships between variables or potential risk factors for emergency hemodialysis.

Declarations

Ethics approval and consent to participate

This study received approval from the ethics committee of Ngoerah Hospital Denpasar.

Competing interests

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Author's Contribution

Idea/concept: KSDS. Design: KSDS. Control/supervision: YK. Data collection/processing: KSDS. Analysis/interpretation: KSDS, YK. Literature review: KSDS. Writing the article: KSDS. Critical review: YK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

The Relationship of Social Support and Spirituality to Resilience in Chronic Kidney Disease Patients Undergoing Regular Hemodialysis at Adam Malik Hospital Medan in 2025

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ABSTRACT

Background: End Stage Renal Disease (ESRD) patients undergoing hemodialysis are faced with demanding long-term therapy that often has a psychological impact. Resilience, the ability to adapt and recover from difficult situations, is an important protective factor for patients to manage medication adherence. External factors, such as social support, and internal factors, such as spirituality, were identified as aspects associated with individual resilience.

Objective: This study aims to analyze the relationship between social support and spirituality on resilience in patients with chronic kidney disease undergoing regular hemodialysis at Adam Malik Hospital, Medan, in 2025.

Methods: This research is an analytic study with a cross-sectional design. Data were obtained through distributing questionnaires at Adam Malik Hospital, Medan, in 2025. Data were processed using the Statistical Package for the Social Sciences (SPSS) software.

Results: Based on the analysis of 50 research samples, it was found that respondents had a high (66%) and a moderate (34%) distribution of resilience. Social support and spirituality have a significant positive relationship with individual resilience.

Conclusion: The majority of PGTA patients undergoing HD at Adam Malik Hospital have high levels of resilience. Social support and spirituality play an important role in increasing individual resilience. Therefore, good social support and spirituality are necessary in order to support treatment compliance, adaptation, and quality of life for HD patients.

Keywords: Resilience, social support, spirituality, hemodialysis, chronic kidney disease.

Introduction

End-stage renal disease (ESRD) is the most advanced stage of chronic kidney disease (CKD), characterized by a progressive decline in kidney function or a glomerular filtration rate (GFR) of less than 15 ml/min in an irreversible manner.[1] Epidemiologically, according to data reports from the Global Burden of Disease, around 10 – 12 million people worldwide suffer from end-stage renal disease.[2] This condition requires long-term management in the form of renal replacement therapy, such as hemodialysis (HD), to maintain patient survival.[3] Hemodialysis remains the most commonly performed renal replacement therapy worldwide, with approximately 89% of dialysis patients receiving it.[4]

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Hemodialysis is a long-term therapy that demands time and lifestyle changes, often causing most hemodialysis patients to experience emotional stress, anxiety, and even depression.[5] In facing these challenges, resilience, or the ability to adapt and recover from difficult situations, becomes a necessary protective factor.[6]

According to Connor & Davidson (2003), external factors such as social support and internal factors such as spirituality are identified as aspects related to individual resilience.[7,8] Social support can provide a sense of safety, love, and appreciation, helping patients adapt more quickly.[9] Meanwhile, spirituality helps patients find meaning and purpose in life and inner peace amid the suffering of chronic illness, thereby directly enhancing individual resilience.[10] This study aims to analyze the relationship between social support and spirituality on resilience in patients with chronic kidney disease undergoing regular hemodialysis at Adam Malik Hospital, Medan, in 2025.

Methods

The research method used was an observational analysis with a cross-sectional study design. The study was conducted at the Hemodialysis Unit of Adam Malik Hospital in Medan from September to October 2025. A sample of 50 individuals was selected using consecutive sampling. Sample measurements and observations were conducted simultaneously, with data collection using a questionnaire. Inclusion criteria included patients aged 18 years or older who had undergone regular HD therapy for at least 3 months, were fully conscious, and could read or write. Exclusion criteria included patients with severe acute clinical conditions or severe cognitive impairment. Resilience levels were measured using the 10-item Connor-Davidson Resilience Scale (CD-RISC) questionnaire, a validated Indonesian version of which was adapted by Perwitasari & Wulandari in 2024.[11] The Multidimensional Scale of Perceived Social Support (MSPSS) questionnaire, developed by Zimet in 1988 and adapted into Indonesian by Winahyu, Hemchayat & Charoensuk in 2015, was used to measure social support.[12,13] Given the respondents' diverse religious backgrounds, the FACIT-Sp12 instrument was used without modifying the questionnaire items. However, to ensure understanding and contextual relevance, the researcher provided verbal clarification to each respondent before completing the questionnaire, adapting the concepts to each respondent's respective teachings. Data analysis was performed using SPSS statistical software. Bivariate analysis used Spearman's Rank correlation test to determine the strength and direction of the relationship between variables. Next, a multivariate analysis using binary linear regression will examine the simultaneous influence of independent variables on resilience.

Results

A The results of the study are shown in Table 1, showing that a large number of respondents were in the pre-senior age group (45-59 years) (28 respondents) (56%), male (30 respondents) (60%), unemployed (34 respondents) (68%), had a high school education (25 respondents) (50%), and had undergone hemodialysis for >12 months (33 respondents) (66%). Respondents also had high levels of social support (35 respondents) (70%), high levels of spirituality (34 respondents) (68%), and high levels of spirituality (33 respondents) (66%).

Table 1. Characteristics of the study population

Characteristics	(N = 50)	%
Age		
Adults (18-44 years)	10	20
Pre-Seniors (45-59 years)	28	56

Elderly (years)	12	24
Gender		
Male	30	60
Female	20	40
Occupation		
Employed	16	32
Not Employed	34	68
Education		
Primary School	3	6
Junior High School	8	16
High School	25	50
College	14	28
Duration of Hemodialysis		
<6 Months	6	12
6-12 Months	11	22
>12 Months	33	66
Social Support		
Moderate Social Support	15	30
High Social Support	35	70
Spirituality		
Moderate Spirituality	16	32
High Spirituality	34	68
Resilience		
Moderate Resilience	17	34
High Resilience	33	66

Spearman's rank correlation was used to assess the strength and direction of the relationship between variables. The decision criterion for this test is a p-value <0.05, indicating a significant relationship or correlation between the two variables.

The test results in Table 2 indicate a positive correlation between social support and resilience, with a strong p-value = 0.000 and r = 0.636. Spirituality also showed a significant positive correlation of moderate strength, with p-value = 0.003 and r = 0.413.

Table 2. Correlation between Social Support, Spirituality, and Sociodemographic Factors

Variable	r	p-value
Social Support	0.636	0.000
Spirituality	0.413	0.003
Age	-0.085	0.558
Gender	0.241	0.091
Education	-0.143	0.322
Occupation	0.141	0.328
Duration of Hemodialysis	-0.245	0.087

Meanwhile, sociodemographic factors, including age, gender, education, occupation, and duration of hemodialysis, did not show a statistically significant relationship with resilience levels (p-values > 0.05).

Binary logistic regression was conducted to examine the effects of multiple independent variables on resilience simultaneously, with $p < 0.05$ as the significance threshold.

The test results in Table 3 indicate that social support and spirituality are significant factors influencing resilience. Social support had a p-value of 0.003 and an OR of 1.372 (CI: 1.112-1.693). This indicates that each increase in the social support score significantly increases the patient's chances of having high resilience by 1.372 times.

Table 3. The Simultaneous Effect of Social Support, Spirituality, and Sociodemographic Factors

		Resilience		n	p	OR (CI)
		Moderate	High			
Social Support	Moderate	12 (24%)	3 (6%)	15 (30%)	0,003	1,372 (1,112-1,693)
	High	5 (10%)	30 (60%)	35 (70%)		
Spirituality	Moderate	10 (20%)	6 (12%)	16 (32%)	0,019	1,563 (1,077-2,269)
	High	7 (14%)	27 (54%)	34 (68%)		
Gender	Male	13 (26%)	17 (34%)	30 (60%)	0,253	3,900 (0,378-40,229)
	Female	4 (8%)	6 (32%)	20 (40%)		
Duration of Hemodialysis	<6 Months	1 (2%)	5 (10%)	6 (12%)	0,270	0,451 (0,110 -1,853)
	6-12 Months	2 (4%)	9 (18%)	11 (22%)		
	>12 Months	14 (28%)	19 (38%)	33 (66%)		

Similarly, spirituality also showed a significant effect, with a p-value of 0.019 and an OR of 1.563 (CI: 1.077-2.269). This means that the higher the spirituality score, the greater the 1.563-fold increase in the odds of having high resilience. Meanwhile, gender and hemodialysis duration did not have a significant effect on resilience (p> 0.05).

Discussion

The majority of patients were in the pre-elderly age group (45-59 years), accounting for 28 patients (56%). This finding aligns with the study by Hustrini et al., which found that PGTA generally affects middle-aged to elderly individuals, with an average patient age of around 48 years. This can be explained by the decline in kidney function with age, due to reduced nephron number, decreased GFR, and increased comorbidities, which are major risk factors for CKD.[14] This study found that the majority of PGTA patients were male (30 patients, 60%). This finding aligns with a study by Francis et al., which stated that the majority of PGTA patients undergoing hemodialysis worldwide are male.[2] The majority of respondents in this study (34, 68%) were unemployed, a finding consistent with Erickson et al., who reported that the demands of hemodialysis therapy limit patients' daily lives and can lead them to stop working.[15]

In this study, the age variable did not significantly influence resilience (p-value = 0.558), indicating that age is not a significant factor in psychological variables such as resilience among hemodialysis patients. This result aligns with the research of Kisomi et al., which stated that hemodialysis patients with good social and spiritual support are able to adapt to their illness, regardless of their age.[16] Similarly, the correlation between unemployment and resilience yielded a p-value of 0.328, indicating no significant

relationship between employment status and resilience levels among hemodialysis patients. This finding aligns with the research of Yan et al. and Erickson et al., which stated that unemployed hemodialysis patients can still have high levels of resilience if they receive good social and spiritual support.[15,17]

In this study, 25 patients (50%) had a high school education. The test for the relationship between education and resilience yielded a p-value of 0.322, indicating no significant relationship between education level and resilience in HD patients. This contrasts with research by Karami, Rahmati, & Abbasi, which found that patients with higher education tend to have greater resilience due to a better understanding of their condition, better problem-solving skills, and access to important information about healthcare services. This relationship was not found in this study.[18]

In this study, 33 (66%) patients undergoing HD had been on hemodialysis for more than 12 months. Bivariate and multivariate tests showed p-values of 0.087 and 0.270, respectively, indicating no significant relationship between hemodialysis duration and patient resilience. Theoretically, a study by Antari explains that one factor that can influence the resilience of hemodialysis patients is the duration of therapy. The longer a person undergoes hemodialysis, the greater the potential for decreased resilience due to physical and mental fatigue, increased complications, and boredom with the long-term therapy routine. However, the results of this study do not directly support this theory.[19]

The majority of patients undergoing regular hemodialysis at Adam Malik Hospital, Medan, had high levels of social support, with 35 (70%) having moderate levels, followed by 15 (30%). Bivariate and multivariate statistical tests showed p = 0.000 and 0.003, respectively, with r = 0.636 and 0.003, indicating a significant relationship between social support and resilience in hemodialysis patients. This research aligns with the theory proposed by Connor & Davidson in Pratiwi & Yuliandri's study, which states that social support is an important aspect in building individual resilience because it makes patients feel cared for, appreciated, and loved by others.[7] High levels of social support from their environment can help kidney patients feel stronger, more energized, more motivated to undergo treatment, and feel well cared for. Patients who feel emotionally and socially supported have a more positive outlook on life, adapt more easily to their physical limitations, and demonstrate better adherence to therapy.[20]

The majority of patients undergoing regular HD at Adam Malik Hospital, Medan, have a high level of spirituality, namely 34 patients (68%), followed by patients with moderate spirituality, totaling 16 patients (32%). The results of the bivariate and multivariate statistical tests showed p-values of 0.003 and 0.019, respectively, and r-values of 0.413 and 0.019, indicating a significant relationship between spirituality and resilience in HD patients. These results are in line with the theory proposed by Zhang et al., which holds that spirituality is a person's ability to find and understand the meaning of life, experience inner peace, and achieve happiness and satisfaction, helping individuals reach their full potential when facing problems due to chronic illness.[10] In the context of hemodialysis patients, spirituality functions as an effective coping mechanism in dealing with stress, anxiety, and uncertainty about the future.[21] Thus, this study's results confirm that spirituality plays an important role in shaping the resilience of hemodialysis patients. Patients who have a strong spiritual connection with God, are able to find meaning in suffering, and undergo the treatment process with sincerity will show better mental resilience.

Conclusion

Based on the research results and discussions conducted on 50 patient respondents, the following conclusions can be drawn: Firstly, the sociodemographic characteristics of the study respondents were pre-elderly (56%), male (60%), had a high school education (50%), were unemployed (68%), and had been on HD for

more than 12 months (66%). Secondly, respondents had high levels of resilience (66%), high levels of social support (70%), and high levels of spirituality (68%). Thirdly, there was a strong relationship between social support and resilience (p = 0.000 and r = 0.636). Fourthly, there was a moderate relationship between spirituality and resilience (p = 0.003 and r = 0.413). Lastly, the levels of social support and spirituality were simultaneously shown to significantly influence resilience (p = 0.003 and 0.019). The researchers also make the following suggestions. Firstly, for future researchers, this study was limited to 50 respondents in one location. Further research is recommended, using a larger sample and multiple hospitals with HD units to obtain more representative results. Secondly, for healthcare professionals, it is recommended to provide more psychosocial support and develop a holistic approach for patients undergoing regular hemodialysis to support adaptation, treatment adherence, and quality of life. Thirdly, for patients, it is recommended that they be more open and actively seek support from family, friends, fellow patients, and healthcare professionals, and increase their spiritual faith. Lastly, for patients' families, it is recommended to consistently provide emotional support, information, and appreciation so that patients feel loved and cared for, thus increasing their optimism during treatment.

Limitations of the Study

This study has limitations: it involved a relatively small sample of 50 respondents. It was conducted at a single location, Adam Malik Hospital, limiting its representativeness of the entire hemodialysis population in Indonesia. This study used a cross-sectional design, in which all variables were measured at a single point in time. Furthermore, as the study was conducted in a hemodialysis unit, respondents' responses may have been influenced by physical or emotional conditions such as fatigue, stress, or discomfort during therapy. This study excluded patients with severe acute clinical conditions or severe cognitive impairment, so the high resilience rate (66%) may not be generalizable to HD patients with these conditions.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee of Adam Malik Hospital.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: DA. Design: DA, BRN, TAN, RACS. Control/supervision: BRN, TAN, RACS. Data collection/ processing: DA. Analysis/interpretation: DA, BRN, TAN, RACS. Literature review: DA, BRN, TAN, RACS. Writing the article: DA. Critical review: BRN, TAN, RACS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Diagnostic Value of Proenkephalin A 119–159 Serum in Early Detection of Sepsis-Associated Acute Kidney Injury

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ABSTRACT

Background: Sepsis-associated acute kidney injury (SA-AKI) is a common condition found in sepsis. Due to the lack of creatinine serum, this condition may delay therapy. Proenkephalin A 119-159 (PENK) is a breakdown product of the prohormone proenkephalin A, which is freely filtered at the glomerulus. On the other hand, this prohormone and its receptor are predominantly expressed in proximal tubular epithelial cells (pTEC) of the kidney. Elevated serum PENK levels are an indicator of AKI. However, previous studies have shown various results.
Objective: This study aims to identify early-detection biomarkers for AKI in sepsis.
Methods: This diagnostic test was conducted at Dr. M. Djamil General Hospital, Padang, in sepsis patients. The diagnosis of AKI was established based on the 2012 KDIGO criteria.
Results: The study involved 98 sepsis patients, 58.16% (n=57) of them experienced AKI. Serum creatinine levels at admission and within 48 hours of hospitalization were 1.0 (IQR 0.8–1.5) mg/dl and 1.6 (IQR 0.9 – 2.1) mg/dl, respectively. A serum PENK level ≥82.6 pmol/L at admission had a sensitivity of 98.6%, a specificity of 95.1%, a positive predictive value of 96.1%, a negative predictive value of 97.5%, and an accuracy of 96.9% in the early detection of AKI in sepsis.
Conclusion: Serum PENK level has excellent diagnostic value in the early detection of AKI in sepsis.
Keywords: Sepsis, proenkephalin A 119–159, AKI.

Introduction

Acute kidney injury (AKI) is a part of the spectrum of acute kidney diseases and disorders characterized by a rapid and significant decline in kidney function due to various potential causes. Clinically, the Kidney Disease Improving Global Outcome (KDIGO) defines AKI as an increase in serum creatinine level ≥0.3 mg/dL within 48

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hours or more than 1.5 times the baseline level. The global incidence of AKI varies from 114 to 174 cases per 10,000 population and occurs in almost all critical illnesses. Among them, sepsis is the main cause in 45–70% cases. A study suggests that AKI events increase the risk of progression to chronic kidney disease (CKD). Early detection and appropriate management could reduce the morbidity and mortality of AKI.[1–3]

Sepsis-associated AKI (S-AKI) is a condition characterized by a rapid decline of kidney function caused by tubular epithelial cell damage and the accumulation of inflammatory cytokines. Zou et al. (2022) reported the increase in creatinine serum level detected 24–36 hours after kidney injury. This limitation makes the creatinine serum unreliable and might be the cause of delayed therapy in unstable settings. Its level is influenced by factors such as age, gender, body fluid volume, and use of diuretics and antihypertensive medications. Finally, in 2023, the 28th Acute Disease Quality Initiative (ADQI) Consensus recommended the use of additional biomarkers to diagnose AKI. Until now, no single biomarker that could replace creatinine serum as the gold standard AKI diagnostic.[4,5]

Proenkephalin A 119-159 (PENK) serum is a potential biomarker to diagnose AKI. PENK has 4,5 kDa weight molecules, unbound with plasma protein, and its levels are not influenced by gender and age. Proenkephalin A is a precursor of PENK. Upon activation, proenkephalin A will be cleaved into active enkephalin peptides such as *met*-enkephalin and *leu*-enkephalin that would be degraded in several minutes. Another cleavage product is an inert peptide called PENK that flows in the vascular until 48 hours. In physiological conditions, active enkephalin binds to delta opioid receptors (DORs), which are found in proximal tubular epithelial cells (PTEC)as cell regulator functions such as diuresis, natriuresis, and inhibition of antidiuretic hormone (ADH). Under injury conditions, proenkephalin will be prepared in cells to adapt to ischemic conditions by reducing cell metabolism and modulating angiogenesis.[6–8]

The use of PENK serum as a diagnostic biomarker for AKI in sepsis has been approved by European Conformity (CE). Multicenter studies in Europe have reported various diagnostic thresholds. In the sepsis population, Rosengvist et al. (2019) reported PENK levels >100 pmol/L, while admission can predict an AKI event 3.5-fold in 48 hours. A study in Germany in 2024 reported that the elevated PENK serum level >89 pmol/L at the time of admission also had good early diagnostic performance. In Asia, similar purpose studies are still limited. Kim et al. (2017) in South Korea reported PENKserum levels linearly with the severity of AKI and sepsis and better diagnostic performance than neutrophil gelatinase-associated lipocalin (NGAL). One similar study was conducted in Indonesia in 2025 with a small population and unsatisfactory results.[5,9,10]

Methods

Design and participants

This study is a diagnostic test using a cross-sectional approach conducted in an inpatient setting in Dr. M. Djamil General Hospital, Padang. Samples were collected from June to December 2025. First, we conducted anamnesis to determine the inclusion and exclusion criteria, and then blood tests were performed. In this study, the sample selection was carried out using consecutive sampling. The sample size was determined by using a particular diagnostic formula, and an optimum sample of 98 people was obtained. The subjects taken as samples were subjects who met the inclusion criteria and were not excluded by the exclusion criteria. The inclusion criteria were sepsis patients with normal serum creatinine levels. While the exclusion criteria were patients with a history of chronic kidney disease (CKD), renal replacement therapy (RRT), acute stroke, acute coronary syndrome, acute heart failure, advanced chronic heart failure, malignancy, hypoalbuminemia, use of diuretics, ACEi or ARB, agonist and antagonist delta opioid receptors (DOR).

Testing of PENK serum was carried out using the Fluoroenzymeimmunoassay (FEIA) method using the AFIAS Penkid Boditech® reagent in the Central Laboratory of Dr. M. Djamil General Hospital, Padang. All samples were grouped into AKI and non-AKI based on KDIGO criteria. Elevated creatinine serum level ≥0.3 mg/dl in 48 hours is defined as AKI, and an elevated level <0.3 mg/dl is defined as non-AKI. The optimal *cut-off* PENK serum level was calculated by the Youden Index in ROC. After that, we conducted diagnostic performance by calculated sensitivy, specificity, negative predictive value, positive predictive value, and accuracy by using Table 2 x 2.

Results

Patient characteristic

This study involved 98% patients with a sepsis diagnosis while admitted. The average age of the sample is 60.5 (IQR 48.8 – 70.0) years old. The proportion of the subgroup geriatric and nongeriatric are relative similar, 53.1% and 46.9%. Then the proportion of females and males are relative similar too, 48% and 52%. Common comorbidities found in this study are diabetes mellitus 33.7%, hypertension 27.6%, chronic heart failure and chronic coronary syndrome 21.4%, and another medical condition 10.2%. Median of the SOFA score at admission is 7. The proportion of subgroups using vasopressor and not using vasopressor is 44.9% and 55.1%. Primary sources of infection are pneumonia 66.3%, skin and soft tissue infection (SSTI) 21.4%, urinary tract infection (UTI) 7.1%, and gastrointestinal hepatobiliary infection 3.1%. Almost 91.9% as a unifocal infection. Median of hemoglobin level at admission is 10.4 (IQR 8.9 – 12.3) gr/dl. The median of the lactate serum level is 1.8 (1.2 – 2.7) mmol/L. Median creatinine levels at admission and after 48 hours of hospitalization are 1.0 (IQR 0.8 – 1.5) mg/dl and 1.6 (IQR 0.9 – 2.1) mg/dl. Besides that, the median of PENK serum levels at admission and after 48 hours of hospitalization are 91.8 (71.1 – 105) pmol/L and 104.4 (71.8 – 245.3) pmol/L. (Table 1).

Table 1. Characteristic of Respondents

Characteristic	n = 98	Characteristic	n = 98
Age, median (IQR)	60,5 (48,8 – 70,0)	**Source infection**, n (%)	
Age Subgroup, n (%)		Pneumonia[1]	65 (66,3)
< 60 years old	46 (46,9)	Skin and soft tissue infection	21 (21,4)
≥ 60 years old	52 (53,1)	Urinary tract infection	7 (7,1)
Sex, n (%)		Gastrointestinal hepatobilliary	7 (7,1)
Males	51 (52,0)	Others[2]	3 (3,1)
Females	47 (48,0)	**Focal infection**, n (%)	
Hospitalization, n (%)		Unifocal	90 (91,9)
Intensive Care Unit	17 (17,3)	Multifocal[3]	8 (9,1)
High Care Unit	81 (82,7)	**Laboratory result**, median (IQR)	
Comorbidites, n (%)		Hb (g/dL)	10,4 (8,9 – 12,3)
Diabetes mellitus	33 (33,7)	Lactate (mmol/L)	1,8 (1,2 – 2,7)
Hypertension	27 (27,6)	Albumin serum (g/dL)	2,8 (2,6 – 3,1)
Chronic heart disease[4]	21 (21,4)	Creatinine serum H_1 (mg/dL)	1,0 (0,8 – 1,5)
Others[5]	10 (10,2)	Creatinine serum H_3 (mg/dL)	1,6 (0,9 – 2,1)
SOFA score, median (IQR)	7 (5 – 10)	PENK serum H_1 (pmol/L)	91,8 (71,1 – 140,5)
Using Vasopresor, n (%)		PENK serum H_3 (pmol/L)	104,4 (71,8 – 245,3)
No	54 (55,1)		
Yes	44 (44,9)		

Description: (1) Pneumonia: includes community-acquired pneumonia and hospitalized-acquired pneumonia, (2) Other sources of infection: includes central nervous system infections, malaria, and leptospirosis, (3) Multifocal: more than one focal infection, (4) Chronic heart disease: includes chronic heart failure and chronic coronary syndrome, and (5) Other comorbidities: includes stroke and chronic liver disease.

Diagnostic Value of Proenkephalin A 119–159 Serum

First, the value of the optimal cut-off of the PENK serum level is calculated by the Youden index. At admission (H_1), PENK serum level ≥82.60 pmol/L is the optimal value with AUC 0.981 (CI 95%; 0.956 – 1.000) and Youden Index 0.934. We also calculated the optimal cut-off after 48 hours of hospitalization (H_3). Its result is ≥85.3 pmol/L with AUC 0.923 (CI95%; 0.926 – 1.000) and Youden Index 0.023. In this study, we found 57 AKI and 41 non-AKI based on the KDIGO criteria. The ROC and diagnostic performances from this study can be found in Table 2 and Figure 1 below.

Table 2. Diagnostic Performance of PENK Serum to Diagnose Sepsis-Associated AKI

Day of Test	PENK (pmol/L)	AKI KDIGO		Sensitivity	Specivity	NPV	PPV	Acuration
		Yes	No					
at Admission (H_1)	≥82.6	56	2	98.2%	95.1%	96.6%	97.5%	96.9%
	<82.6	1	39					
48 hours in hospitalization (H_3)	≥85.3	54	1	94.7%	97.6%	98.2%	93.0%	95.9%
	<85.3	3	40					

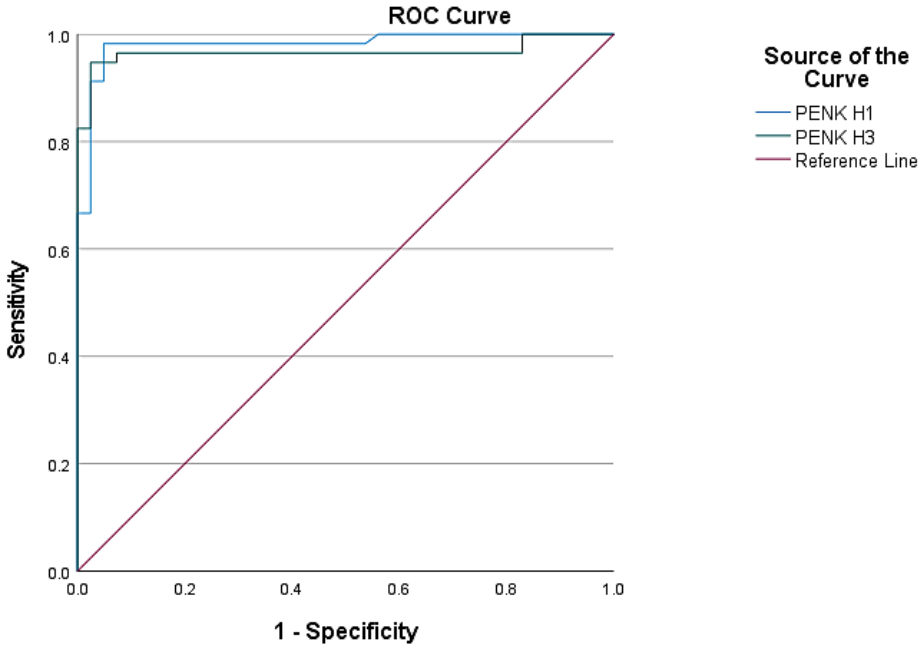

Figure 1. Receiver Operation Curve (ROC)

Discussion

In this study, we reported that PENK serum has excellent diagnostic performance for the early detection of AKI in sepsis patients. While creatinine serum was normal at admission, elevated PENK serum level more than 82.60 pmol/L resulted sensitiviy 98.2%, specivity 95.1%, negative prediction value 96.6%, positive prediction value 97.5%, and accuration 96.9% (AUC 0.981). This result is consistent with the multicenter study in Germany, 2020 – 2022. Martin et al. (2025) reported elevated PENK level more than 100 pmol/L in 910 critically ill patients, while creatinine serum was normal at admission, had better diagnostic performance than creatinine serum (AUC 0.880 vs 0.74). Another multicenter study in Germany was conducted by Schulte et al. (2024). Increased PENK serum level more than 89 pmol/L at admission in 529 sepsis patient result good diagnostic performance with sensitivity 72%, specificity 83%, positive predictive value 77%,

and negative predictive value 79% (AUC 0.870).[11,12]

A Study in the Asian population reported similar results. Ji et al. (2025) documented 41% AKI in 161 septic patients in China. PENK serum level more than 241 pmol/L resulted in good performance with sensitivity 0.79 and specificity 0.83 (AUC 0.880). Another study in Bangladesh conducted by Hassan et al. (2025) reported elevated PENK serum level of more than 145 pmol/L resulted in fair performance with a sensitivity 67.9% and specivity 98.3% (AUC 0.796). Based on this result, we concluded elevated PENK serum level, while a normal creatinine serum level at admission, could be a tool for early diagnosis of AKI in sepsis patients. Compared with previous studies, we revealed a higher diagnostic value. It might have caused more exclusion criteria to be used. We have excluded conditions that might affect PENK level, such as an acute cardiac or stroke event. Meanwhile, in previous studies, they only excluded CKD, gravid, and palliative states.[13,14]

Determination of the threshold PENK serum level for detecting AKI in the general population is a challenge. In addition, until now, there is no reference normal PENK level in healthy people. These facts might be caused by the limitations of the studies about this topic. Since it started 2 decades ago, multicenter studies have focused in Europe population. Malmö Diet and Cancer Study (MDCS) in Sweden documented that the healthy PENK serum level is 46.34 (SD±14,6) pmol/L. Genomic analysis resulted in PENK serum level distinguished by polymorphism rs1012178 that located on chromosome 8. Every minor changed T allel would increase 0.057 pmol/L of PENK. But there is no global data reported on the variability of that polymorphism among populations.[15]

There are two studies that reported the association of PENK serum level with ethnicity and race. The Impact of Migration and Ethnicity on Diabetes in Malmö (MEDIM) in Sweden reported the determination of PENK level with deterioration of kidney function. Although by similar PENK level between the Swedish and Middle Eastern ethnic groups (71.1 and 70 pmol/L) and a significant traditional risk of CKD in the Middle Eastern ethnic group, deterioration of kidney function is greater in the Swedish ethnic group. The Reasons for Geographic and Racial Difference in Stroke (REGARDS) study in the USA reported insignificantly different PENK levels in the healthy kidney population of black and white races. The medians of PENK level are 62.6 (IQR 48.9 – 73.9) pmol/L and 56.2 (IQR 46.7 – 70.1) pmol/L. It is assumed that the effect of the genetic factor is the renal protective effect of PENK.[16,17]

Besides the genetic factor, another factor that might have affected the PENK level is heart condition. Historically, clinical studies about PENK were started in the 1980s in the heart failure population. Postmortem study reported the amount of DOR and vesicle proenkephalin A at postsynaptics of cardiac autonomous nerve (CAN) and tubulus transversalis of cardiomyocytes. Another study revealed that every release of a norepinephrine vesicle was accompanied by a proenkephalin A vesicle. Overactivation of the sympathetic nerve was well-known as characteristic of acute heart failure and advanced chronic heart failure. This emphasized the function of PENK as cardioprotective by the contraregulatory sympathetic effect. It is quite understandable that PENK levels was usual significanly increased in these diseases.[18]

Matsiras et al. (2025) described the reason for the increased PENK level in the heart failure population. It was still related to kidney dysfunction. In case of reduced ejection fraction (HfrEF), it was clearly understable and affected by hypoperfusion. In preserved EF, dyastolic dysfunction will increase central venous pressure (CVP) and concomitantly the vena cava. This condition will cause intraglomerular hypertension (renal tamponade) and ultimately affect kidney function. Because PENK freely filtrates in the glomerulus, increasing PENK level in the heart failure population is assumed to be caused by kidney dysfunction.[18]

Study of Emmen et al. (2019) emphasized that the main factor of increased PENK level in heart failure population is kidney dysfunction. Compared with cardiac biomarker (NT-pro BNP, troponin, LVEF) and renal biomarkers (eGFR, urine NGAL, urine KIM), increased PENK level is the strongest association with eGFR. Every increased PENK 40 pmol/L linearly associated with a 1.29-fold increased risk of AKI. Another Great Network Study reported that increased of PENK level of more than 97.2 pmol/L in the AHF population linearly associated with a 1.58-fold risk of AKI. However, in this study, we tried to exclude the heart failure factor by anamnesis without echocardiography findings.[19,20]

In a sepsis patient-based study, PENK levels might be affected by the severity of disease and inflammation, but it is still inconclusive. Verras et al. (2024) reported moderate correlation between PENK levels and creatinine serum (rho 0,327) and procalcitonin level (rho 0,527) and mild correlation with lactate serum (rho 0,369) and SOFA score (rho 0,391). On the other hand, a study by Frigyesi et al. (2021) reported that in 632 patients with sepsis, PENK levels are only correlated with renal and cardiovascular SOFA. There is no correlation with other SOFA components such as respiration, hepatic, neurological, and coagulation function. Another study in the sepsis population emphasized that the increased of PENK levels significantly occurred in AKI. Hassan et al. (2021) reported in a serial test (admission, 2nd, and 7th days of hospitalization) between AKI and non-AKI subgroups, PENK levels only significantly increased in the AKI population (159,4±78,7 pmol/L, 332,6±89,2 pmol/L, and 478,2±98,4 pmol/L). In non-AKI subgroups, serial test PENK level was relatively constant (69,4±32,9 pmol/L, 65,9±30,2 pmol/L, and 75,3±36,7 pmol/L).[14,21,22]

In addition to early diagnosis, the PENK serum level test could determine AKI severity. In critically ill patients, Martin et al. (2025) reported the mean of PENK serum level in AKI grade 1 is 56 (IQR 44 – 76) pmol/L and in AKI grade 2/3 is 88 (64 – 163) pmol/L. In the subgroup with renal replacement therapy, the PENK level was higher, 108 (55 – 142) pmol/L. Facts that lack of study in Indonesia and other potential of PENK in kidney dysfunction were expected to be the background to conduct further research.[11]

Conclusion

PENK serum level test has excellent diagnostic performance for early detection of sepsis-associated AKI.

Limitations of the Study

This study was conducted in a referral hospital. Most of the participants had already received vasopressor therapy or antibiotics, which may be nephrotoxic. Consequently, it is difficult to determine whether the tubular damage was a direct or indirect consequence of sepsis. Furthermore, advanced chronic heart failure, which could affect PENK levels, was only excluded from medical history without real-time echocardiography.

Declarations

Ethics approval and consent to participate

This study was conducted after obtaining ethical approval from the Health Research Ethics Committee of Dr. M. Djamil Padang General Hospital, Number: DP.04.03/D.XVI.10.1/201/2025.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: AW. Design: AW. Control/supervision: DP, DV, HH, NN, RK, RBS, AWM. Data collection/ processing: AW. Analysis/interpretation: AW, DP, DV, HH, NN, RK, RBS, AWM. Literature review: AW, DP, DV, HH, NN, RK, RBS, AWM. Writing the article: AW. Critical review: AW, DP, DV, HH,

NN, RK, RBS, AWM. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Seroprevalence of CMV and HSV in Kidney Transplant Donor Candidates and Recipients at Ngoerah Hospital, Denpasar

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ABSTRACT

Background: Despite significant advancements in solid organ transplantation over recent decades, infections remain a leading cause of morbidity and mortality among transplant recipients. Herpesviruses, particularly Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV), are the most common viral pathogens affecting this patient population.

Objective: This study aims to evaluate the seroprevalence of CMV and HSV infections among kidney transplant donor and recipient candidates at RS. Ngoerah Denpasar.

Methods: This descriptive study involved 66 adult subjects, comprising 33 kidney transplant donor candidates and 33 recipient candidates, all aged over 18 years. The study participants were evaluated for CMV and HSV seroprevalence using serological tests, including IgG and IgM antibodies, to determine the presence of latent or active infections. The study population included patients with chronic kidney disease (CKD) stage V who were candidates for kidney transplantation.

Results: Among the 33 donor candidates, 39.4% were found to have both CMV and HSV infections, with 45.5% testing positive for IgG anti-CMV, indicating a latent CMV infection. In the recipient candidate group, 27.3% were infected with both CMV and HSV, with 42.4% showing seropositivity for IgG anti-CMV. Additionally, a small proportion of donor and recipient candidates were found to have reactivated HSV infections, as indicated by the presence of IgM antibodies. The study highlights the significant prevalence of CMV and HSV infections among kidney transplant donor and recipient candidates.

Conclusion: These findings underscore the importance of thorough serological screening prior to transplantation to identify latent infections that may influence post-transplant outcomes.

Keywords: Seroprevalence; Cytomegalovirus; Herpes Simplex Virus; Kidney Transplantation; Donor Screening.

Introduction

Despite the rapid development of solid organ transplantation in recent decades, infections remain a major cause of morbidity and mortality among solid organ transplant recipients. The herpesvirus family is the most common viral pathogen causing disease in this patient population. Herpesviruses are large enveloped DNA viruses that commonly reactivate during periods of severe immunosuppression. Currently, infections caused by herpesviruses complicate the clinical management of transplant patients. Two viruses belonging to this family are Cytomegalovirus (CMV) and Herpes simplex virus (HSV). This study aimed to assess the

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seroprevalence of CMV and HSV infections in kidney transplant candidates and recipients.[1]

CMV is a herpesvirus found in 40%-70% of the population, is common after solid organ transplantation, and is an independent risk factor for graft loss and mortality. Iatrogenic immunosuppression targeting T cells can result in uncontrolled CMV replication.[2] The risk of CMV infection in the first month after transplantation is generally minimal, despite the high-intensity immunosuppression used at the time of transplantation due to the lack of prolonged immunosuppressive exposure. The duration of immunosuppressive exposure is thought to be an important factor in the development of opportunistic infections such as CMV.[3–5] In a study of 5000 kidney transplants in one health center, the incidence of CMV infection in the first 30 days after kidney transplantation was 0.2%. Common clinical findings in patients were bleeding requiring reoperation and prolonged cold ischemic time (CIT). The outcomes of CMV infection in the first 30 days and later were similar. The study concluded that the results of the study can provide clinicians with information as a basis for confidence that the overall risk of CMV infection in the first 30 days is very low.[2]

HSV has 2 types, namely HSV type 1 and HSV type 2 (HSV-1, HSV-2), which belong to the alpha-herpesvirus family. These viruses are characterized by a short replication cycle, rapid growth in culture, host cell lysis during replication, and latency in nerve ganglia. Although HSV-1 and HSV-2 share 40% of their nucleotide sequence, they have distinct epidemiological profiles, biological features, and antigenic features.[1] The majority of the population is infected with HSV-1 during childhood or early adolescence via saliva. Primary infection is usually asymptomatic or presents as gingivostomatitis, while reactivation of the virus usually results in herpes labialis. Transmission to humans occurs through direct contact with lesions or secretions of an actively shedding person. The prevalence of HSV-1 in the United States has been reported to be 80% by age 60 years. HSV-2 infection is less common, usually acquired through sexual transmission and is usually associated with genital infections. The prevalence of HSV-2 infection increases with age, with prevalence rates in the United States for 14-19 and 40-49 year-olds being 1.6% and 26.3%, respectively.[6] Colitis in solid organ transplantation is more commonly caused by CMV than HSV.[7]

Screening of potential organ donors and recipients before transplantation is an essential part of solid organ transplantation. The goals of pretransplant infectious disease screening are as follows: (1) to identify donor or recipient eligibility; (2) to identify and treat active pretransplant infections; (3) to determine the level of risk for infection to determine posttransplant infection prevention strategies.[8] CMV serologic status of the donor and recipient is an important predictor of post-transplant events, with CMV-seronegative recipients of CMV-seropositive (D+/R-) donor organs being at greatest risk for developing tissue-invasive CMV, recurrent CMV, and ganciclovir-resistant CMV. However, D+/R- status is not generally considered a contraindication to transplantation, but rather an indication for a more intensive posttransplant monitoring and prevention strategy. Seropositive recipients, regardless of donor status, are also at risk for CMV and usually receive pre-emptive prophylaxis or monitoring. HSV screening is performed in some centers, while others do not perform screening but provide universal antiviral prophylaxis for at least the first month posttransplant.[8,9]

Methods

This study used a descriptive research design involving 66 samples, namely recipients (33 patients) and donors (33 patients) from the adult population aged >18 years at Ngoerah Hospital, Denpasar. The target population in this study were patients with chronic kidney failure (CKD) stage V who had become candidates for kidney transplant recipients and candidates for kidney organ donors. The accessible population in this study were patients who were candidates for kidney transplant recipients and donors who underwent procedures at Ngoerah Hospital, Denpasar. The sample of this study was candidate

donors and recipients who would undergo kidney transplantation and met the inclusion and exclusion criteria. The inclusion criteria in this study were patients aged >18 years, as candidates for kidney donors or recipients who were diagnosed with CKD stage V, and agreed to participate in the study by providing written informed consent, while the exclusion criteria in this study were incomplete patient data.

Results

The total subjects included in this study were 66 people, with 33 (50.0%) patients as donor candidates and 33 (50.0%) patients as recipient candidates, of which 12 (18.2%) were male, and 21 (31.8%) were female from the donor candidate group. The number of male subjects from the recipient candidate group was 22 (33.3%) and female subjects from the recipient candidate group were 11 (16.7%). The majority of patients were in the age group of 50-59 years and 60-69 years in the donor candidate group. (N=13; 19.7%), and in the recipient group were aged 18-29 years (N=15; 22.7%).

The majority of causes of CKD were chronic glomerulonephritis (GNC) (N=27; 40.9%). Subjects with candidate recipient status had chronic kidney failure (CKD) stage V. Most of the kidney transplant recipient candidates underwent renal replacement therapy in the form of hemodialysis (N=30; 45.5%). The majority of recipients underwent renal replacement therapy for 1 year (N=17; 25.8%) (Table 1).

Table 1. Subject characteristics

Characteristics	**Patient Status (%)**	
	Donor (n = 33)	**Recipient (n = 33)**
Age (years)		
- 18-29	2 (3.0)	15 (22.7)
- 30-39	0 (0.0)	14 (21.2)
- 40-49	5 (7.6)	3 (4.5)
- 50-59	13 (19.7)	0 (0.0)
- 60-69	13 (19.7)	1 (1.5)
Mean ± SD (Age)	52.4 ± 9.1	31.2 ± 10.8
Gender		
- Male	12 (18.2)	22 (33.3)
- Female	21 (31.8)	11 (16.7)
Etiologic of CKD		
- PNC	0 (0.0)	3 (4.5)
- GNC	0 (0.0)	27 (40.9)
- Nefrosclerotic	0 (0.0)	1 (1.5)
- DKD	0 (0.0)	1 (1.5)
- SN	0 (0.0)	1 (1.5)
- No CKD	33 (50.0)	0 (0.0)
Stage of CKD		
- V	0 (0.0)	33 (50.0)
- No CKD	33 (50.0)	0 (0.0)
Kidney Replacement Therapy		
- Hemodialysis	0 (0.0)	30 (45.5)
- Peritoneal dialysis	0 (0.0)	1 (1.5)

- Predialysis	0 (0.0)	1 (1.5)
- Unknown	0 (0.0)	1 (1.5)
- No CKD	33 (50.0)	0 (0.0)
Duration of Replacement Therapy (years)		
- <1	0 (0.0)	2 (3.0%)
- 1-3	0 (0.0)	25 (37.9%)
- 4-7	0 (0.0)	3 (4.5%)
- Unknown	0 (0.0)	3 (5.5%)
- No CKD	33 (50.0)	0 (0.0)
Mean ± SD (Therapy Duration)	N/A	1.67 ± 1.2

From the 33 patients with kidney transplant candidate donor status, 26 (39.4%) had CMV and HSV infections, while 6 (9.1%) had CMV infections only. A total of 30 (45.5%) patients in the candidate donor group had anti-CMV IgG seropositivity, while 2 (3.0%) had anti-CMV IgG and anti-CMV IgM seropositivity. IgG anti-HSV 1 seropositivity was found in 24 (36.4%) patients in the candidate donor group. IgG anti-HSV 1 seropositivity and IgM anti-HSV 1 seropositivity were found in 2 (3.0%) patients in the candidate donor group. Seronegative for HSV was found in 7 (10.6%) patients in the candidate donor group (Table 2).

Table 2. Seroprevalence of CMV and HSV in kidney transplant donors and recipients.

Variable	Patient Status		*p-value*
	Donor (N=3)	Recipient (N=33)	
Serology			0.042*
- HSV	0 (0.0)	1 (1.5)	
- CMV	6 (9.1)	13 (19.7)	
- CMV, HSV	26 (39.4)	18 (27.3)	
- Seronegative	1 (1.5)	1 (1.5)	
CMV			0.435
- Long-standing/latent infections	30 (45.5)	28 (42.4)	
(IgG +, IgM -)	2 (3.0)	2 (3.0)	
- Reactivation (IgG +, IgM +)	0 (0.0)	1 (1.5)	
- Acute infections (IgG -, IgM +)	1 (1.5)	2 (3.0)	
- Non-reactive (IgG -, IgM -)			
HSV 1			0.171
- Long-standing/latent infections	24 (36.4)	17 (25.8)	
(IgG +, IgM -)	2 (3.0)	2 (3.0)	
- Reactivation (IgG +, IgM +)	0 (0.0)	0 (0.0)	
- Acute infections (IgG -, IgM +)	7 (10.6)	14 (21.2)	
- Non-reactive (IgG -, IgM -)			

HSV 2			0.052
- Long-standing/latent infections	8 (12.1)	2 (3.0)	
(IgG +, IgM -)	0 (0.0)	0 (0.0)	
- Reactivation (IgG +, IgM +)	0 (0.0)	2 (3.0)	
- Acute infections (IgG -, IgM +)	25 (37.9)	29 (43.9)	
- Non-reactive (IgG -, IgM -)			

*p<0.05: significant relationship

In the candidate recipient patient group, out of 33 people, 18 (27.3%) experienced CMV and HSV infections, while 13 (19.7%) others only experienced CMV infections. There was 1 (1.5%) person in the candidate recipient group who experienced HSV infection. IgG anti-CMV seropositivity was found in 28 (42.4%) patients in the candidate recipient group, while IgG anti-CMV and IgM anti-CMV were found positive in 2 (3.0%) patients. IgM anti-CMV seropositivity was found in 1 (1.5%) patient in the candidate recipient group. Seropositivity for IgG anti-HSV 1 was found in 17 (25.8%) patients in the candidate recipient group, while seropositivity for IgG anti-HSV 1 and IgM anti-HSV 1 was found in 2 (3.0%) patients in the candidate recipient group, while seronegative for HSV was found in 14 (21.2%) patients in this group (Table 2).

Discussion

Cytomegalovirus (CMV) is a member of the Herpesviridae family that is known to be a major pathogen in patients with compromised immune systems, such as solid organ transplant recipients, hematopoietic cell transplant recipients, patients infected with Human Immunodeficiency Virus (HIV), and individuals undergoing immunomodulatory therapy. Although CMV infection is often asymptomatic in immunocompetent individuals, it can cause serious complications in immunosuppressed populations. In immunocompromised patients, the clinical manifestations of CMV are very diverse and can include unexplained febrile syndrome, hepatitis, pneumonitis, retinitis, encephalitis, esophagitis, and colitis. These complications not only worsen the patient's clinical condition but also potentially increase the risk of mortality if not treated adequately.[7]

The diagnosis of CMV infection is often challenging, especially because the signs and symptoms that appear can resemble other viral infections. Establishing a diagnosis of CMV requires a comprehensive approach, including evaluation of the patient's clinical history, careful physical examination, and confirmation by laboratory tests involving direct detection of the virus or through signs of viral activity. One of the major challenges in diagnosis is differentiating between latent infection, asymptomatic reactivation, and active CMV disease. Latent infection is a condition in which the virus remains in the body without causing symptoms, but can replicate again when the patient's immune system is weakened, causing reactivation that has the potential to progress to clinical disease.[10]

The terms "CMV infection" and "CMV disease" have important differences in clinical contexts. CMV infection refers to the presence of a virus in the body, which can be detected through virus isolation, detection of viral proteins (antigens), or their nucleic acids in body fluids or tissue specimens, even if no symptoms appear. In contrast, CMV disease refers to a condition in which a CMV infection causes noticeable clinical symptoms, as mentioned above. It is important for clinicians to differentiate between the two because treatment approaches and patient management differ based on whether the patient only has CMV infection or has developed CMV disease.[8]

Studies to determine the cut-off between CMV infection and disease have been conducted, with varying results. A study in Brazil found that a threshold value of 5010 copies/mL OF CMV DNA in the blood can be used to distinguish infections from CMV disease, although its sensitivity and specificity are not yet fully optimal.

Another study reported a lower threshold, which was 3800 copies/mL, with a sensitivity of 76.9% and a specificity of 91.6%. However, this variability suggests that there is no one universally reliable threshold, and clinical decisions often need to be tailored to the patient's specific context, including immunity status and other clinical conditions. By understanding the complexities of CMV infection diagnosis and management, clinicians can reduce the risk of serious complications in immunocompromised patients, as well as improve long-term outcomes post-transplant or in the management of immunosuppression-related diseases.[7,8]

Screening of donors and potential organ recipients before transplantation is a very crucial component of the solid organ transplant process. This process aims not only to ensure that the donor and recipient are in decent health, but also to identify and treat infections that may be present before the transplant takes place. The main objectives of pre-transplant infectious disease screening include three important aspects: first, to ensure the feasibility of donor and recipient conditions; second, identifying and managing existing active infections in the pre-transplant phase; and third, assessing the level of infection risk to develop effective post-transplant infection prevention strategies.[6]

The serological status of CMV of donors and recipients has an important role as a predictor of the risk of posttransplant complications. Recipients who are seronegative for CMV, but receive organs from donors who are seropositive for CMV (D+/R-), are at the highest risk of developing CMV infections that can be invasive, cause tissue damage, and even become recurrent or resistant to antiviral treatments such as gancyclovir. In this scenario, although D+/R- status increases the risk of posttransplant complications, this condition is not considered an absolute contraindication to transplantation. Instead, this status demands a more intensive and targeted monitoring and prevention strategy after transplantation.[11,12]

Prevention strategies that may be applied to recipients with seronegative status who receive organs from seropositive donors may include the use of long-term antiviral prophylaxis or pre-emptive monitoring approaches. Antiviral prophylaxis, such as gancyclovir or valgancyclovir, are generally given during the first 3 to 6 months posttransplant to reduce the risk of primary CMV infection. In addition, the pre-emptive monitoring approach involves routine monitoring of the viral load of CMV via PCR or other serological methods, with therapeutic interventions initiated immediately after virus detection, even if no clinical symptoms have yet emerged.[13,14]

Meanwhile, recipients who are already seropositive for CMV, regardless of the donor serological status, are also at risk of CMV reactivation. This risk necessitates the application of similar prophylaxis or pre-emptive monitoring, especially in the early post-transplant period when immunosuppression is at its peak. Prophylaxis in this group not only lowers the risk of primary or recurrent CMV infection, but also helps prevent further complications that can affect the long-term outcomes of the transplant, such as decreased graft function or even graft loss.[2,15]

In addition to CMV, screening for other infections such as Herpes Simplex Virus (HSV) is also important, although practices vary across different transplantation centers. Some health centers perform serological screening for HSV, while others prefer to administer universal antiviral prophylaxis, such as acyclovir or valacyclovir, to all recipients for at least the first month post-transplant. This prophylactic approach aims to reduce the risk of HSV reactivation, which can occur in recipients who are severely immunosuppressed.[13,16]

However, screening and treatment are not limited to CMV and HSV. Other active viral infections, such as hepatitis virus or community-acquired respiratory viruses, should also be considered. If an active viral infection is detected in a potential recipient, the decision to delay the transplant is often wiser until the infection improves. This delay allows the recipient's body to develop a natural immune response before

intensive immunosuppression is administered, which is an integral part of the transplant protocol.[2]

A similar approach is also applied to transplant candidates who show clinical symptoms leading to acute viral infections. Delaying transplantation in this situation not only helps in the recovery of the recipient's health condition, but also gives time for the transplant team to develop a more effective prevention strategy. These recommendations support a more cautious and targeted approach to managing the risk of infection before, during, and after solid organ transplantation.[8]

Overall, pre-transplant infectious screening and post-transplant infection risk management require a personalized approach based on each patient's risk profile. Careful attention to the patient's serological status and clinical condition allows the transplant team to minimize the risk of infection and ensure better outcomes for posttransplant patients. The strategy should be flexible and adapted to the development of the patient's condition, while taking into account the latest evidence and existing clinical guidance.[9]

Cytomegalovirus (CMV) infection is one of the major challenges in posttransplant management, especially in patients with high-risk serostatus. The main risk factors known to affect the occurrence of CMV infection include the patient's serostatus before transplantation and the presence of decreased lymphocyte count, which is an important marker in the immune system. Decreased lymphocytes, specifically T cells, may facilitate the reactivation of latent CMV or worsen primary infections, given the central role of T cells in controlling viral replication. When lymphocytes are significantly reduced due to immunosuppression used in transplants, the risk of CMV infection increases substantially.[11,17]

In addition, gender and impaired kidney function have also been identified as risk factors for CMV infection. A study showed that men had a higher risk of developing post-transplant CMV infection, with a hazard ratio (HR) of 1.92. This may be related to immunological differences between the sexes, where males tend to have different immune responses compared to females. In addition, decreased glomerular filtration rates, measured through estimated glomerular filtration rate (eGFR), were also found to be a risk factor with an HR of 0.98. A decrease in eGFR indicates more severe kidney damage, which can affect the body's ability to handle infections, including CMV.[13]

One of the interesting findings is the variability of CMV strains that can affect clinical outcomes in recipients who are seropositive for CMV. In patients with seropositive CMV status who receive kidneys from donors who are also seropositive (D+/R+), there is a possibility of pseudoprimary infection. This pseudoprimary infection occurs when a recipient who already has antibodies to CMV is re-exposed to a different strain of CMV from the donor, which can lead to reactivation of the infection with higher virulence. This condition is often associated with poorer clinical outcomes compared to recipients who receive kidneys from seronegative donors (D-/R+), where there is no exposure to new CMV strains.[1,8,10]

However, not all studies conclude that CMV seropositivity always has a negative impact. A retrospective cohort evaluating the high prevalence of CMV IgG antibodies found no significant association between CMV disease and the risk of death or graft loss in kidney transplant recipients. These findings suggest that although CMV may increase the risk of complications, not all patients with seropositive CMV will experience poor outcomes. Other factors, such as immunosuppression management and the use of antiviral prophylaxis, are also likely to play a role in influencing long-term outcomes.[6,9,11]

Nevertheless, other studies have shown that rapid episodes of deteriorating clinical conditions, often due to CMV infection, can significantly increase the risk of graft loss and long-term mortality. Uncontrolled CMV infection, especially in the early posttransplant period, can cause severe damage to graft tissue as well as interfere with the function of the newly

transplanted kidney. Therefore, close monitoring and early intervention are essential to prevent complications that can have long-term consequences.

The study conducted by Strivastava et al. provides further insight into the risk of CMV infection in recipients who receive kidneys from donors with D+/R+ status. This study showed that recipients who did not receive routine CMV prophylaxis were more susceptible to late CMV infection. These infections are often invasive and destructive, which directly affects graft function and is associated with poor long-term outcomes. This emphasizes the importance of antiviral prophylaxis in high-risk patients, especially in those with D+/R+ status.[10,11]

Antiviral prophylaxis, as recommended in various clinical guidelines, aims to suppress CMV replication during the critical post-transplant period. Without prophylaxis, the risk of reactivation of CMV or primary infection can increase, which can trigger serious complications such as pneumonia, gastroenteritis, and even other life-threatening diseases. In recipients with D+/R+ status, long-term antiviral prophylaxis is often necessary to reduce this risk, and regular viral load monitoring can help detect CMV replication at an early stage.[15]

Overall, the management of CMV infections in kidney transplant recipients is complex and requires a personalized approach. Identification of risk factors such as serostatus, lymphocyte decrease, sex, and eGFR is essential for assessing individual risk and designing effective prevention strategies. With proper monitoring and the timely use of antiviral prophylaxis, the risk of complications due to CMV infection can be minimized, thereby increasing the chances of long-term success of kidney transplantation.[13]

Herpes Simplex Virus (HSV) infection has complex and unique infection mechanisms, especially in the context of primary infection and reactivation. During primary infection, HSV replicates in the mucocutaneous layer, such as the skin or mucous membranes, which is where the virus first enters and begins its life cycle. The virus then moves retrogradely through the axons of sensory neurons to the nerve ganglion, where it settles in a latent state. This latent state allows the virus to hide from the immune system and survive in the body for the lifetime of the infected individual.[14,18]

Although there have been many studies on the pathogenesis of HSV, to date, there is no effective method to stop or control viral latency at the cellular molecular level. This latency is one of the biggest challenges in the management of HSV infection, as the virus can remain dormant for years and then undergo reactivation, especially when individuals experience a decline in immune systems, such as in organ transplant recipients.[5,6,9]

HSV reactivation is generally endogenous, meaning that the virus that has been dormant in the body for a long time becomes reactivated, rather than the occurrence of a new exogenous infection from the outside. This reactivation can be triggered by a variety of factors, including stress, illness, or immunosuppression that is often used in organ transplant patients. In kidney transplant recipients, the risk of HSV reactivation is significantly increased due to the use of immunosuppressive drugs necessary to prevent organ rejection, but it can also weaken the immune system that protects against latent viral reactivation.[15]

Although rare, there have been reports of transmission of HSV through kidney transplant grafts. This occurs when the donor has an active or latent HSV infection, and the virus is transmitted to the recipient through the transplanted organ. This is one of the reasons why screening for infectious diseases in organ donors is so important, even though HSV infection is usually considered less critical compared to other infections such as CMV.[13]

Studies assessing the seroprevalence of HSV-2 in kidney transplant recipients provide important insights into the spread of this infection among patients with immuno-

suppression. In the study, it was found that 5.4% of kidney transplant recipients had anti-HSV-2 IgG antibodies, indicating prior or latent infection with HSV-2. Interestingly, these patients did not show clinical manifestations of genital herpes, which is the most common form of HSV-2 infection. This suggests that HSV-2 infection in transplant recipients may often be subclinical or clinically undetectable, although the presence of this virus can have significant clinical implications, especially in the event of reactivation.[19]

The study also noted that there was no significant association between HSV-2 seropositivity and factors such as age, sex, history of hemodialysis and transplantation, blood transfusions, or immunosuppression regimens used. These findings suggest that HSV-2 infection in kidney transplant recipients may be more influenced by other factors, such as the individual's immunity status or previous exposure to the virus, rather than demographic or clinical variables typically considered.[20]

Although HSV-2 is often associated with genital herpes, in the kidney transplant recipient population, the clinical manifestations of the infection may be more varied or unclear. HSV reactivation can lead to a wide range of complications, ranging from mild mucocutaneous lesions to more serious diseases such as meningoencephalitis or hepatitis, especially in patients with severe immunosuppression. Therefore, although the prevalence of HSV-2 infection may appear low, it is important for clinicians to remain vigilant of possible reactivation and associated complications in kidney transplant recipients.[21]

In the management of transplant recipients, the prevention and control of HSV reactivation is generally carried out through antiviral prophylaxis. Medications such as acyclovir or valacyclovir are used routinely in the early posttransplant period to prevent reactivation of herpesvirus infections, including HSV. The administration of this prophylactic is especially important in patients who are known to have seropositivity against HSV, as they have a higher risk of experiencing reactivation of the infection.[21,22]

Overall, although HSV infection may appear to be less dangerous than other infections such as CMV, the potential complications it poses in kidney transplant recipients should not be underestimated. A comprehensive approach to screening, prevention, and management of HSV infection is needed to ensure that the risk of viral reactivation and its clinical impact can be minimized, thereby improving long-term outcomes for posttransplant patients.[2,23]

If antiviral prophylaxis is not given, the risk of infection in solid organ transplant recipients increases significantly, with an estimated 40-50% of them developing infection within the first month post-transplant. In this period, clinical manifestations of infections, including Herpes Simplex Virus (HSV), generally appear within 2-3 weeks after transplantation, coinciding with the intensive phase of immunosuppression administered to prevent organ rejection. This condition shows how critical the administration of antiviral prophylaxis is in preventing opportunistic infections that can threaten patient safety in the early posttransplant phase.

HSV, in particular, has the ability to reactivate quickly after the start of immunosuppression therapy. This risk of reactivation and infection is greatly influenced by the intensity of immunosuppression administered. Powerful immunosuppressive drugs, such as OKT3 (anti-CD3 monoclonal antibody), mycophenolate mofetil, or anti-thymocyte globulin, are known to be associated with high rates of HSV reactivation. Studies show that patients who receive this therapy have a higher risk of developing severe HSV disease, including mucocutaneous and visceral complications.[20]

Gingivostomatitis, a condition in which HSV causes inflammation of the gums and oral mucosa, is more commonly found in patients undergoing hematopoietic cell transplants than solid organ transplant recipients. However, solid organ recipients are also susceptible to other

forms of HSV infection, such as anogenital herpes, which is usually caused by HSV-2. HSV-2 can undergo reactivation from latent conditions in the sacral ganglia, especially when the immune system is suppressed by immunosuppression therapy. Although these mucocutaneous infections are often considered mild, they can cause significant morbidity, especially if left untreated.[16,18,19]

Without therapeutic intervention, HSV can spread and cause much more serious complications. For example, in patients with uncontrolled HSV infections, especially those with HSV-induced hepatitis, mortality rates can reach 60%-80%. In the most severe cases, when the infection causes intravascular coagulopathy to be disseminated, mortality can be close to 100%. In these situations, a liver transplant may be necessary for patients who have fulminant liver failure due to HSV infection. These extreme cases highlight the importance of aggressive and timely management of HSV infection in this highly vulnerable patient population.[21]

The use of antiviral drugs such as acyclovir, valacyclovir, and valgancyclovir has been shown to be effective in preventing most HSV reactivations. This antiviral prophylaxis should be an integral part of the management of solid organ transplant patients, especially for those who have been identified as seropositive against HSV-1 or HSV-2. In cases where the patient does not receive antiviral prophylaxis against CMV (Cytomegalovirus), special consideration should be given to initiating prophylaxis against HSV, given the high risk of reactivation and the complications that can occur.[23]

Some researchers also argue that HSV prophylaxis may also be necessary in patients with seronegative HSV, although this evidence still requires further confirmation. This approach is based on the potential risk of HSV primary infection which can be particularly severe in individuals who are severely immuno-suppressed.[21]

The efficacy of HSV prophylactic administration has been proven in various studies, particularly in recipients receiving OKT3. Administration of acyclovir, which is the standard of therapy, is recommended at a dose of 400-800 mg twice daily for at least the first month posttransplant. In patients with a history of severe HSV reactivation, higher doses may be necessary to prevent further reactivation. In addition, dosage adjustments should be made based on the patient's kidney function, since the clearance of this drug is highly dependent on kidney function. Kidney failure can lead to drug accumulation and increase the risk of toxicity, so close monitoring and careful dosage adjustment are essential.[11,20]

In conclusion, the administration of antiviral prophylaxis should be considered a key element in posttransplant protocols to prevent potentially fatal opportunistic infections such as HSV. A coordinated and personalized approach in immunosuppression management and infection prevention can improve overall clinical outcomes and reduce morbidity and mortality in solid organ transplant recipients. Thus, the integration of comprehensive prevention strategies into clinical practice can provide significant protection for patients in the critical post-transplant phase.[20,29]

Conclusion

This study evaluated the seroprevalence of Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV) infections in donor candidates and kidney transplant recipients in hospitals. Ngoerah Denpasar. The results showed that among the donor candidates, as many as 39.4% were infected with both CMV and HSV, with 45.5% of them showing anti-CMV IgG seropositives, indicating latent CMV infection. In addition, some donor candidates also showed seropositive for anti-HSV-1 IgG, with a small proportion showing viral reactivation characterized by the presence of anti-HSV-1 IgM. On the other hand, in the recipient candidate group, as many as 27.3% were infected by CMV and HSV. Of this group, 42.4% showed anti-CMV IgG

seropositives, signaling a latent infection that may require special posttransplant attention. Some recipients also showed seropositive for anti-HSV-1 IgG and anti-HSV-1 IgM, indicating a risk of postoperative infection reactivation. The conclusion of this study confirms the importance of serological screening before kidney transplantation to detect the presence of latent infections that can affect post-transplant clinical outcomes. By knowing the serological status of CMV and HSV in donors and recipients, medical teams can implement more targeted and intensive prevention strategies, especially in high-risk recipients, to reduce the likelihood of complications of post-transplant infection. This is important to improve the long-term success of kidney transplants and maintain the health of postoperative patients.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee of the Ngoerah Hospital, Denpasar.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: NNAT. Design: NNAT. Control/supervision: IKS, YK. Data collection/ processing: NNAT. Analysis/interpretation: NNAT. Literature review: NNAT. Writing the article: NNAT. Critical review: IKS, YK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Review Article

New Guideline for Chronic Kidney Disease 2024, What Primary Care Can Do About It?: A Narrative Review

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ABSTRACT

Background: Chronic Kidney Disease (CKD) presents an urgent global public health crisis, affecting over 850 million people worldwide, with low-income nations like Indonesia facing a high burden of undiagnosed cases due to limited awareness and a deficient primary care system.
Objective: This paper serves as a vital, practical response to the novelty of the KDIGO 2024 Clinical Practice Guideline update, which incorporates a decade of new evidence, including the ethical imperative to eliminate the ethnic coefficient from eGFR equations and the introduction of consensus-based "Practice Points."
Methods: This narrative review synthesizes the updated KDIGO 2024 Clinical Practice Guideline for the evaluation and management of CKD.
Results: Key findings from this review highlight that CKD diagnosis is not solely reliant on Glomerular Filtration Rate (GFR), but also on persistent markers of kidney damage such as albuminuria and urine sediment abnormalities. The 2024 updates strongly recommend the ethnicity-free CKD-EPI 2021 equation for routine screening, the use of estimated GFR based on creatinine and cystatin C (eGFRcr-cys) for superior accuracy, and the strong recommendation for Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) in Type 2 Diabetes patients with CKD. Additionally, the guidelines introduce actionable risk prediction thresholds for nephrology referral, alongside practical advice like "sick day rules" for primary care.
Conclusions: It concludes that primary care, as the frontline in health services, must rapidly adopt these standards to enhance early screening, improve patient risk stratification, and facilitate timely, informed referrals to advanced care, thereby mitigating disease progression and improving patient outcomes globally.
Keywords: Chronic Kidney Disease, eGFR, KDIGO, Primary Care.

Introduction

The 2024 Kidney Disease Improving Global Outcomes (KDIGO) guideline updates optimizes services and applications of the latest science for Chronic Kidney Disease (CKD) patients.[1,2] Significant changes that 6 statements were left from the guideline in 2012 and updated both the approach to diagnosis, risk stratification to services for CKD patients.[1] Chronic Kidney Disease defined as abnormalities of kidney structure OR function, present for a minimum of 3 months, with implication for health.[1] Globally, in 2017, a systematic analysis found the prevalence of CKD to be 9.1% (8.5%-9.8%) with 697.5 million cases of CKD at all stages.[3] As of 2021, data from multiple international collegia of specialists revealed that there were over 850 million cases of

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kidney disease worldwide, nearly twice as many as patients with diabetes (422 million) and 20 times more than those with cancer (42 million) or HIV (36.7 million).[1] A multicenter study at a tertiary health service in Jakarta, Indonesia, from December 2021 to July 2022 found 1,152 patients with kidney failure.[4] This demonstrates that a rise in kidney disease cases, particularly CKD, is expected to occur for a number of reasons, including lifestyle choices and other factors.

Kidney illness is thought to affect 850 million people globally, with the majority residing in lower-middle-class and low-income nations (for example, Indonesia). In settings with limited resources and a deficient primary care system, up to 90% of people with CKD are not aware that they have the disease and do not seek treatment.[5] In a country like Indonesia, the role of primary care is needed for CKD cases, because the community, in addition to the lack of awareness of CKD and the lack of accessibility of primary care, is a cause of the increase in CKD cases in low-income countries. Therefore, Primary care, as the frontline in health care, needs to update its capacity and capability towards CKD through the guideline update of KDIGO 2024. This is because primary care will be the first place patients come before they can get referrals to advanced hospitals. Hence, it is important for primary care doctors to be familiar with the updates of KDIGO 2024 as well as the identification (screening) of CKD patients in primary care so that they can be referred more quickly to get complete health services.

CKD IN NOWADAYS: UPDATES FROM KDIGO 2024

The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD[1] significantly updates its 2012 predecessor,[2] incorporating a decade of new evidence to provide more precise guidance. A key methodological enhancement is the introduction of "Practice Points", which are consensus-based expert statements offering practical guidance for clinical questions lacking systematic reviews or to aid the implementation of graded recommendations. Unlike the "Not Graded" statements in KDIGO 2012,[2] Practice Points are now recognized as important expert guidance, not a lesser form of recommendation. Both guidelines maintain the CGA (Cause, GFR category, Albuminuria category) classification system for CKD, with KDIGO 2024[1] reinforcing its widespread acceptance and utility in guiding management and risk assessment. For assessing kidney function, while creatinine-based eGFR (eGFRcr) remains the initial assessment, KDIGO 2024 now strongly recommends (1B) the use of estimated GFR based on both creatinine and cystatin C (eGFRcr-cys) when cystatin C is available, citing its superior accuracy in diagnosis and staging of CKD and emphasizing understanding the implications of differences between eGFRcr and eGFRcys. Notably, the updated guideline explicitly advises against using ethnicity in eGFR computation.[1]

A major leap in KDIGO 2024 lies in risk prediction for kidney failure.[1] The guideline now strongly recommends (1A) employing externally validated risk equations to estimate the absolute risk of kidney failure in individuals with CKD G3–G5, establishing actionable thresholds for care. For instance, a 5-year kidney failure risk of 3–5% prompts nephrology referral, a 2-year risk >10% suggests multidisciplinary care, and a 2-year risk >40% indicates the need for kidney replacement therapy (KRT) modality education and transplant planning. Pharmacologically, Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) are a significant addition, strongly recommended (1A) for adults with Type 2 Diabetes and CKD with an eGFR ≥20 mL/min/1.73 m^2, continuing even if eGFR falls lower.[1] Non-steroidal mineralocorticoid receptor antagonists (MRA) are also suggested for high-risk T2D patients with persistent albuminuria, with careful potassium monitoring. While KDIGO 2012 found insufficient evidence for uric acid-lowering to delay CKD progression, KDIGO 2024 now recommends (1C) uric acid-lowering for symptomatic hyperuricemia, but not for asymptomatic cases, to slow progression. Updates also include nuanced guidance on RAS inhibitor use, such as investigating >30% eGFR

decrease rather than immediately stopping for creatinine increases.[1]

The 2024 guideline introduces a dedicated chapter on medical management and drug stewardship, underscoring the necessity of periodic medication reviews, particularly during care transitions. A key practical update includes "sick day rules," advising planned temporary discontinuation of specific medications (e.g., SGLT2i, ACEi, ARBs, metformin) before elective surgery or during acute illness, coupled with clear communication on when to restart to mitigate harm. This promotes patient education on medication benefits and risks and encourages collaboration with pharmacists. Regarding optimal models of CKD care, the guideline reinforces the value of team-based, multidisciplinary care, providing specific risk-based criteria for initiating such comprehensive support. It further addresses modern care delivery, including the integration of telehealth technologies for patient education and remote monitoring, and offers detailed guidance on the transition of care for young people moving from pediatric to adult nephrology services. These updates collectively foster a more patient-centered, integrated, and evidence-based approach to CKD management, aiming to improve outcomes globally.[1]

DETECTION OF CKD, IS IT ONLY RELYING ON GFR?

According to KDIGO 2024, CKD is diagnosed when evidence of kidney damage or decreased kidney function persists for a minimum duration of three months. The diagnosis can be based on either one or more markers of kidney damage or a reduction in glomerular filtration rate (GFR). Markers of kidney damage include albuminuria (albumin-to-creatinine ratio [ACR] > 30 mg/g or > 3 mg/mmol), urine sediment abnormalities, persistent hematuria, electrolyte and other abnormalities attributable to tubular disorders, histological abnormalities, structural abnormalities identified by imaging, or a history of kidney transplantation. Alternatively, CKD can also be diagnosed when there is a decreased GFR of less than 60 ml/min/1.73 m^2 (corresponding to GFR categories G3a–G5), even in the absence of other markers of kidney damage, provided that this reduction is sustained for at least three months.[1]

Albuminuria is one of the critical markers in the detection, evaluation, and management of CKD. It refers to the presence of albumin in the urine. Under normal circumstances, the kidneys filter waste products while retaining essential proteins like albumin in the bloodstream. When the kidneys' filtering units (glomeruli) are damaged, they may allow albumin to leak into the urine, resulting in albuminuria.[1]

Building upon this understanding, numerous studies have consistently recognized albuminuria as a fundamental marker for diagnosing and managing CKD. According to the American Academy of Family Physicians (AAFP), persistently elevated serum creatinine and albuminuria serve as diagnostic and prognostic hallmarks of CKD, with even low levels of albuminuria being associated with adverse renal and cardiovascular outcomes.[6] Similarly, the Clinical Journal of the American Society of Nephrology highlights that glomerular filtration rate (GFR) and albuminuria are the primary measures for detecting, staging, and managing both acute and chronic kidney disease.[7] Furthermore, recent literature reinforces albuminuria as a strong indicator of kidney damage and a predictor of disease progression and cardiovascular complications.[8] Collectively, these findings emphasize its pivotal role in CKD assessment and care.

To standardize its application in clinical practice, albuminuria levels are categorized and interpreted to determine CKD stage and evaluate the risk of disease progression. According to KDIGO guidelines, albuminuria is classified into:

Table 1. Albuminuria Severity Grade[1]

Category	AER	ACR (approximately equivalent)		Terms
	(mg/24 h)	(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased
A3	>300	>30	>300	Severely increased

Higher levels of albumin in urine have been strongly linked to an increased risk of CKD progression and cardiovascular events, including coronary artery disease, stroke, and heart failure (Barzilay JI et al., 2024).[9] Monitoring albuminuria allows for patient risk stratification, guiding treatment decisions and determining appropriate follow-up intervals, as reductions in albuminuria have been shown to correlate with slower CKD progression and a lower likelihood of progression to end-stage kidney disease.[10] Furthermore, a significant decrease in albuminuria, such as a 50% reduction, may indicate a favorable response to therapeutic interventions, including the use of renin-angiotensin system inhibitors, and is associated with a notable reduction in cardiovascular risk and heart failure incidence.[11] Conversely, a doubling of the albumin-to-creatinine ratio (ACR) on follow-up testing surpasses normal laboratory variability and has been associated with a higher incidence of CKD stage 4-5, thereby warranting further clinical evaluation.[12]

While albuminuria provides significant insight into kidney damage and its potential progression, it is equally important to consider other diagnostic markers, such as urine sediment abnormalities, which complement albuminuria in forming a more comprehensive picture of renal health. Urine sediment abnormalities refer to the presence of atypical elements in the urine, such as red and white blood cells, casts, crystals, and microorganisms, which are typically identified through microscopic examination after centrifugation. These abnormalities serve as an important diagnostic marker for CKD, as defined by the KDIGO 2024 Clinical Practice Guideline, which states that CKD is characterized by structural or functional kidney abnormalities persisting for more than three months. Analyzing urine sediment can help identify underlying causes, such as red blood cell casts indicating glomerulonephritis, white blood cell casts suggesting interstitial nephritis or pyelonephritis, and granular casts associated with acute tubular necrosis.[1]

This foundational understanding of urine sediment abnormalities naturally extends to the broader recognition of their diagnostic value in nephrology. Urine sediment analysis, microscopic examination of abnormal elements in urine such as blood cells, casts, crystals, and microorganisms, has long been regarded as a valuable diagnostic tool. Perazella (2015) highlights that this method remains an effective urinary biomarker, capable of detecting kidney disease and providing critical information about the specific compartment of renal injury.[13] Similarly, Cavanaugh (2019) emphasizes that urine sediment examination continues to serve as a classic, information-rich approach to kidney disease evaluation.[14] Furthermore, the American Family Physician (2017) clinical guideline recommends the use of urine sediment analysis when intrinsic kidney disease is suspected.[6]

Urine sediment analysis not only aids in discerning underlying renal pathologies but is also invaluable for diagnosis and prognosis in clinical practice. Indeed, Perazella (2015) underscores

that sediment examination "alerts the clinician to the presence of kidney disease and provides diagnostic information that often identifies the compartment of kidney injury".[13] Cavanaugh (2019) similarly maintains that it "remains a time-honored test that continues to provide substantial information about the patient's underlying kidney disease". Practical data further reinforce its utility: when nephrologists conduct urine sediment examinations versus automated lab analysis, they more accurately detect pathologic casts and dysmorphic red blood cells, achieving near-perfect diagnostic and prognostic accuracy for conditions like acute tubular injury and glomerulonephritis compared to a kidney biopsy.[15] These findings highlight that urine sediment assessment is a highly specific and powerful tool in the accurate diagnosis and longitudinal evaluation of CKD, justifying its role as an indispensable component of kidney disease work-ups.

Building upon the diagnostic strength of urine sediment analysis, a comprehensive evaluation of CKD also necessitates functional assessment, where estimated glomerular filtration rate (eGFR) plays a pivotal role. Estimated glomerular filtration rate (eGFR) is one of the critical markers in the detection, evaluation, and management of CKD. It is a calculated value that approximates the rate at which the kidneys filter waste from the blood, expressed in milliliters per minute per 1.73 square meters of body surface area (mL/min/1.73 m^2). It is derived from serum creatinine levels, age, sex, and ethnicity, providing a practical assessment of kidney function. eGFR aids in risk stratification for CKD progression and related complications.[1]

Table 2. Glomerular Filtration Rate (GFR) Grading[1]

GFR category	GFR (ml/min/per 1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

While the KDIGO 2024 guidelines recommend using externally validated risk equations to estimate the absolute risk of kidney failure in individuals with CKD stages G3–G5—such as identifying a 5-year kidney failure risk of 3%–5% to inform nephrology referral, eGFR and the urine albumin-to-creatinine ratio (ACR) remain foundational for both disease staging and management. eGFR influences treatment decisions such as initiating SGLT2 inhibitors in type 2 diabetes with CKD and eGFR ≥20 mL/min/1.73 m^2, while regular monitoring of eGFR is vital for tracking progression, assessing therapeutic efficacy, and adjusting care plans as needed.[1]k

While eGFR and ACR remain core parameters for staging and guiding the management of CKD, they are most effective when interpreted alongside other diagnostic indicators that reflect underlying renal pathology. Among these, persistent hematuria serves as an

early marker of glomerular injury, often preceding measurable changes in kidney function and adding further depth to risk stratification. Persistent hematuria represents one of the earliest clinical indicators of underlying glomerular disease, often preceding measurable declines in kidney function.[16] Evidence shows that even mild or moderate microscopic hematuria is associated with an increased risk of CKD progression and mortality, underscoring its diagnostic value in identifying subclinical renal injury and initiating early management strategies.[17]

Beyond glomerular involvement, tubular disorders may present with electrolyte and acid-base abnormalities such as hyperkalemia or metabolic acidosis, which reflect impaired tubular function. Research indicates that these disturbances not only serve as markers of renal damage but can also precede significant reductions in glomerular filtration rate (GFR), making early recognition crucial to slow disease progression through corrective interventions.[18]

Histopathological assessment through kidney biopsy remains the gold standard for diagnosing structural renal abnormalities, including interstitial fibrosis and glomerulosclerosis, which carry strong prognostic implications for CKD progression.[19] Complementing histological evaluation, non-invasive imaging modalities such as ultrasound, CT, and MRI provide critical insights into renal morphology, enabling detection of structural abnormalities like cystic disease or congenital malformations before overt functional decline.[20]

Furthermore, individuals with a history of kidney transplantation represent a unique population in which close surveillance for CKD markers is essential, given their elevated risk of graft dysfunction and recurrent disease. Early identification of abnormalities in this group allows timely therapeutic adjustments and improves long-term graft survival.[21]

Table 3. Pros and cons of kidney markers

Parameter	Pros	Cons
Albuminuria	- Strong predictor of CKD progression and cardiovascular events[22] - Cost-effective in targeted screening, low cost[23,24]	- Biological and analytic variability (exercise, fever, UTI) → repeat testing needed[1]
Urine sediment	- Detects casts/dysmorphic RBCs for localizing injury[25] - Recommended for suspected intrinsic disease[25] - Low cost[15]	- Operator-dependent[25]
eGFR	- Core for staging, drug dosing → primary marker for determining the stage of CKD and is used to adjust drug dosages to prevent toxicity in patients with impaired kidney function.[1] - Accuracy improves with cystatin C or 2021 CKD-EPI[26] - Cost: Low (creatinine)[27]	- Creatinine influenced by age, sex, muscle mass, diet, and tubular secretion[27] - Cost: Moderate (cystatin C)[28]

Electrolyte and acid-base abnormalities	- Reveal tubular dysfunction; low bicarbonate linked to faster CKD progression[29] - Cost: Low - moderate[29]	- This is a non-specific clinical and diagnostic sign that typically appears in the later stages of disease and cannot be used alone to establish a definitive diagnosis.[30]
Structural abnormalities	- USG: Detects obstruction, cysts, cortical changes[20] - CT/MRI: High sensitivity for masses, stones, and complex cysts[20] - Cost: USG: Low - moderate[20]	- USG: Operator - dependent[20] - CT/MRI: Radiation/contrast risk[20] - MRI: Often requires sedation[20] - Cost: Moderate - high (CT)[20] - Cost: High (MRI)[20]

Collectively, these diagnostic markers, including hematuria, tubular disorders, histological abnormalities, imaging findings, and post-transplant monitoring, establish a comprehensive framework for the early detection and longitudinal assessment of CKD. This integrated approach underscores the importance of combining conventional markers such as serum creatinine (SCr), estimated glomerular filtration rate (eGFR), and albuminuria with point-of-care testing (POCT), standardized laboratory assessments, and risk-prediction tools (e.g., QKidney, Kidney Health Australia Risk Test). Additional measurements, including urinary albumin-creatinine ratio (ACR), microalbuminuria (MAU), proteinuria, cystatin C, and emerging biomarkers, further enhance diagnostic precision, enabling timely interventions to preserve renal function and improve patient outcomes.[31]

EVALUATION WITH GFR, WHICH EQUATION WE SHOULD USE?

The accuracy of eGFR equations relies heavily on their input biomarkers. Creatinine, while cheap and ubiquitous, is flawed by its dependence on muscle mass, necessitating age and sex adjustments. It also suffers from a "blind spot" due to tubular secretion and susceptibility to drug interference.[1,32] Conversely, Cystatin C is biologically superior; produced constantly by all nucleated cells and independent of muscle mass, it offers greater accuracy for the elderly and those with altered body composition. Additionally, the difference between cystatin and creatinine estimates ("eGFRdiff") strongly predicts cardiovascular mortality.[33] However, widespread adoption is limited by high costs, restricting Cystatin C primarily to confirmatory testing.

For nearly five decades, the Cockcroft-Gault (C-G) equation underpinned pharmacokinetic dosing. However, its reliance on total body weight has rendered it dangerous in an era of rising obesity prevalence, as it systematically overestimates clearance in patients with high adiposity, leading to potential drug toxicity.[32] The 2024 FDA Guidance effectively ended the clinical relevance of C-G, recommending contemporary eGFR equations for drug development.[34] This shift paved the way for the MDRD and CKD-EPI 2009 equations, which standardized assays and introduced Body Surface Area (BSA) indexing. While the CKD-EPI 2009 equation became the global gold standard for its improved precision at higher GFRs, it retained an ethnic coefficient that adjusted estimates upward for Black patients, a feature that would eventually be challenged on ethical grounds.[35]

The definition of superiority underwent a radical re-evaluation with the 2021 reports from the NKF-ASN Task Force. Recognizing that ethnicity is a sociological construct rather than a biological determinant, the Task Force recommended the immediate adoption of the CKD-EPI 2021 Creatinine (ethnicity-free) Equation.[32] This transition was driven by the

imperative to eliminate systemic racism in medicine; the removal of the ethnic coefficient ensures that Black patients are not systematically disqualified from transplant waitlists due to artificially inflated eGFR values.[36] While this refitting resulted in a slight loss of statistical precision for non-Black populations—leading to minor overestimation of GFR—the nephrology community has largely accepted this trade-off, prioritizing health equity and the standardization of care over marginal statistical gains.[37] Studies indicate that approximately 45.8% of Black adults with CKD stages 3–5 would be reclassified to a more severe stage using the 2021 equation, directly impacting clinical management.[38]

While the US focused on equity, European researchers targeted the "age-gap" problem, the disjointed transition between pediatric and adult equations that disrupts longitudinal care. The European Kidney Function Consortium (EKFC) developed a novel equation utilizing a "Q-value" (median normal creatinine for age/sex) to create a seamless continuum from age 2 to over 90.[35] Validation studies suggest that the EKFC equation may be mathematically superior in European and East Asian cohorts, particularly in the elderly, where it avoids the overestimation bias seen with CKD-EPI.[39] The narrative of a "universal" equation fractures further when applied to Asian populations. The anthropometric differences in muscle mass-to-BSA ratios mean that Western-derived equations often fail in Japan, China, and South Asia. For instance, the CKD-EPI 2021 equation significantly overestimates GFR in Japanese populations, necessitating the use of the specific Japanese Society of Nephrology (JSN) equation to prevent the massive underdiagnosis of CKD.[1] Similarly, validation studies in Pakistan indicate that locally derived equations (PK-CKD-EPI) significantly outperform global models, underscoring that biological validation must precede clinical implementation in diverse ethnic groups.[40] In China, the BIS (Berlin Initiative Study) equation has shown promise for the elderly, further complicating the choice of a single standard.[41]

The comprehensive analysis of current literature indicates that no single equation holds universal superiority; rather, the "best" equation is contingent upon the clinical context. From a purely scientific perspective, the CKD-EPI 2021 Creatinine-Cystatin C Combined Equation is unequivocally the most accurate mathematical model. By integrating two biomarkers with disparate non-GFR determinants, it cancels out individual errors, yielding the highest P30 accuracy (>90%) and the most robust risk prediction.[42]

In the realm of public health, particularly within the United States, the CKD-EPI 2021 Creatinine (ethnicity-free) Equation reigns superior for routine screening. This approach successfully balances the operational requirement of using a low-cost biomarker with the ethical mandate to eliminate ethnic-based health disparities. Finally, regarding pharmacological applications, the BSA-Unindexed CKD-EPI 2021 equation has emerged as the superior method for drug dosing, replacing the flawed Cockcroft-Gault equation to ensure safer dosing in patients with extremes of body size.[34]

WHAT PRIMARY CARE CAN DO ABOUT CKD?

Early detection of CKD is essential to prevent disease progression and adverse outcomes. Screening should target individuals at elevated risk based on well-established predispositions. These include patients with diabetes mellitus (type 1 and 2), hypertension, cardiovascular disease, including a history of heart attack or stroke, obesity, autoimmune disorders like lupus or IgA nephropathy, history of recurrent kidney stones or chronic urinary tract infections (UTIs), and a family history of CKD or kidney failure. Additionally, individuals aged ≥ 60 years and those of African, South Asian, or Hispanic background carry a higher risk, as do those who are exposed to nephrotoxic agents, such as long-term NSAIDs, calcineurin inhibitors, or radiographic contrast, or environmental toxins like heavy metals or industrial solvents. Kidney transplant recipients also represent a high-risk group warranting

vigilant monitoring. Clinical indicators for evaluation include persistent hematuria or proteinuria, eGFR < 60 mL/min/1.73 m², uncontrolled hypertension, fatigue, and electrolyte or acid–base disturbances without alternative explanations (KDIGO 2024).[1,43–45]

Screening for these high-risk individuals involves periodic assessments of eGFR (preferably creatinine-based, with cystatin C if available) and urine albumin-to-creatinine ratio (uACR), backed by risk prediction tools such as QKidney or the Kidney Health Australia calculator to enhance five-year risk identification (KDIGO 2024).[1,31] A CKD diagnosis is confirmed when markers, such as albuminuria, urine sediment abnormalities, structural changes on imaging, or sustained eGFR decline, persist for at least three months.[1] Once diagnosed, CKD management requires a multifaceted approach: lifestyle modifications (healthy diet, exercise, weight control, and smoking cessation), blood pressure control with target <120/80 mm Hg using renin-angiotensin inhibitors, individualized glycemic targets for diabetes patients, and use of SGLT2 inhibitors (particularly in type 2 diabetes patients with eGFR ≥ 20 mL/min/1.73 m²) due to their renal and cardiovascular benefits.[1]

Ongoing monitoring of eGFR and uACR (at least annually or more frequently in high-risk cases) is critical. A greater-than 20% eGFR decline or a doubling of ACR between tests exceeds expected variability and should prompt further clinical action.[1] Referral to a nephrologist is warranted in cases of rapid progression, refractory hypertension, substantial albuminuria, or in anticipation of renal replacement therapy. Finally, patient education and shared decision-making empower individuals to understand CKD, adhere to treatment, and participate actively in their care, ultimately improving outcomes and preserving kidney function. By implementing these strategies, primary care physicians can significantly impact the early detection, effective management, and prevention of CKD progression, ultimately improving patient outcomes.

As for implementation in Indonesia, Cystatic C and uACR were not widely available. This test is considered vital for diagnosing and assessing the patient's current condition. A potential solution is to request the provision of this test in primary health care, supported by the government. However, for the Indonesian government to approve this, a valid cost-effectiveness study is certainly required. Therefore, a multicenter study involving health economists, public health experts, and nephrologists is vital to demonstrate the cost-effectiveness and long-term benefits of this test in slowing the progression of CKD cases. Whilst awaiting the results of the research, primary care facilities may refer these patients for routine monitoring of Cystatin C and uACR levels, as these are key parameters for monitoring the patient's condition. As general practitioners in healthcare settings, it is essential to understand the role and monitoring of Cystatin C and uACR, so that this data is not merely recorded but used to inform further patient management.

Conclusion

The KDIGO 2024 Clinical Practice Guideline marks a crucial inflection point in CKD management, synthesizing a decade of evidence into an integrated, ethically-driven framework. A key finding is the imperative to adopt a multi-marker approach for diagnosis, moving beyond sole reliance on Glomerular Filtration Rate (GFR) to include persistent markers of kidney damage such as albuminuria and urine sediment abnormalities. For functional assessment, the guidelines strongly advocate for the ethnicity-free CKD-EPI 2021 equation for routine screening to advance health equity, and the combined Creatinine-Cystatin C equation for superior accuracy when available. Pharmacologically, the strong recommendation for SGLT2 inhibitors in Type 2 Diabetes patients with CKD introduces a potent therapeutic tool for renoprotection. This review directly addresses the critical research gap concerning the primary care sector's capacity and capability to implement these global standards. We conclude that primary care, as the indispensable frontline of health

services, must rapidly assimilate these KDIGO 2024 updates. By doing so, primary care physicians can significantly enhance early screening, refine patient risk stratification, and ensure timely, informed referrals to specialist care, thereby effectively mitigating disease progression and improving patient outcomes in high-burden, resource-limited settings globally.

Declarations

Competing interests

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Author's Contribution

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Case Report

Ruptured Renal Artery Aneurysm in a Young Man with Uncontrolled Hypertension: Renovascular Implications in Nephrology Clinical Practice

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ABSTRACT

Renal artery aneurysm (RAA) is a rare renovascular condition that may represent both a consequence of long-standing hypertension and an underrecognized cause of secondary hypertension, particularly in young patients. A 23-year-old man with a four-year history of poorly controlled hypertension (peak blood pressure 170/100 mmHg) presented with acute left flank pain. On admission, blood pressure was 154/110 mmHg with severe anemia (hemoglobin 6.3 g/dL), preserved renal function (creatinine 1.18 mg/dL), and mild proteinuria (1+) without hematuria. Contrast-enhanced CT angiography demonstrated a 2.54-cm saccular RAA (Rundback type I) arising from the left renal artery, accompanied by a large perirenal hematoma measuring 8.3 × 6.7 × 14.2 cm, consistent with rupture. The patient had been taking intermittent captopril 12.5 mg once daily prior to admission. Selective endovascular coil embolization using a 3.3-mm VortX coil via right femoral access was successfully performed, achieving complete aneurysm exclusion with preserved renal perfusion. This case highlights the bidirectional relationship between hypertension and RAA. Chronic hypertension likely contributed to aneurysm formation, while intrarenal hemodynamic disturbances may have activated the renin-angiotensin-aldosterone system (RAAS), leading to secondary hypertension. The marked improvement in blood pressure following intervention supports a reversible renovascular mechanism. RAA should be considered in young patients with uncontrolled or resistant hypertension. Early vascular imaging and timely endovascular management are essential to prevent life-threatening complications and address reversible renovascular hypertension.

Keywords: Renal artery aneurysm, renovascular hypertension, endovascular treatment, young adult.

Introduction

Renal artery aneurysm (RAA) is an uncommon manifestation of renovascular disease, defined as a localized dilatation involving all layers of the arterial wall. Despite its low prevalence, the increasing use of computed tomography angiography (CTA) and magnetic resonance angiography (MRA) has improved detection rates, leading to more frequent identification of RAAs, even in asymptomatic individuals.[1,2]

RAA represents a unique entity with a bidirectional relationship with hypertension. Chronic elevation of intraluminal pressure promotes vascular remodeling and weakening of the arterial wall, predisposing to aneurysm formation.[1,3] Conversely, RAAs may contribute to hypertension through altered renal perfusion, turbulent blood flow, and activation of the renin–angiotensin–aldosterone system (RAAS).[3]

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Although many RAAs remain asymptomatic, they may present with nonspecific symptoms such as flank pain, hematuria, abdominal discomfort, or poorly controlled hypertension. In rare but severe cases, rupture may result in retroperitoneal hemorrhage.[3] This report highlights a rare presentation of ruptured RAA in a young patient and provides clinical evidence of a reversible renovascular hypertension component following endovascular intervention.

Case Presentation

A 23-year-old man presented with a sudden onset of severe left flank pain lasting approximately 12 hours, accompanied by low-grade fever and a sensation of fullness in the left upper abdomen. He had a four-year history of poorly controlled hypertension, with a peak recorded blood pressure of 170/100 mmHg, and poor adherence to follow-up. His prior medication consisted of intermittent captopril 12.5 mg once daily. There was no history of kidney disease, abdominal trauma, bleeding disorders, or systemic illness. On admission, the patient was hemodynamically stable with a blood pressure of 154/110 mmHg and a heart rate of 98 beats per minute. Physical examination revealed a tender, pulsatile mass in the left upper quadrant of the abdomen (Figure 1). Laboratory evaluation demonstrated severe anemia (hemoglobin 6.3 g/dL), preserved renal function (serum creatinine 1.19 mg/dL), and mild proteinuria (1+) without hematuria. Electrolytes were within normal limits.

Figure 1. Abdominal examination revealed a mass in the left upper quadrant

Contrast-enhanced CT angiography revealed a 2.54-cm saccular aneurysm arising from the main left renal artery, classified as Rundback type I, with a large perirenal hematoma measuring 8.3 × 6.7 × 14.2 cm, consistent with rupture (Figure 2). No evidence of renal artery stenosis or imaging features suggestive of fibromuscular dysplasia was observed.[4,5]

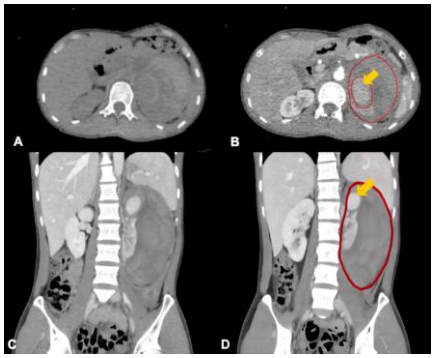

Figure 2. Abdominal CT angiography showing a ruptured left renal artery aneurysm (yellow arrow) with a large perirenal hematoma (red line) (A&B axial view; C&D coronal view)

Emergency endovascular management was performed using selective coil embolization via right femoral arterial access with a 3.3-mm VortX coil. Post-procedural angiography demonstrated complete exclusion of the aneurysm with preserved perfusion to the remaining renal parenchyma (Figure 3).

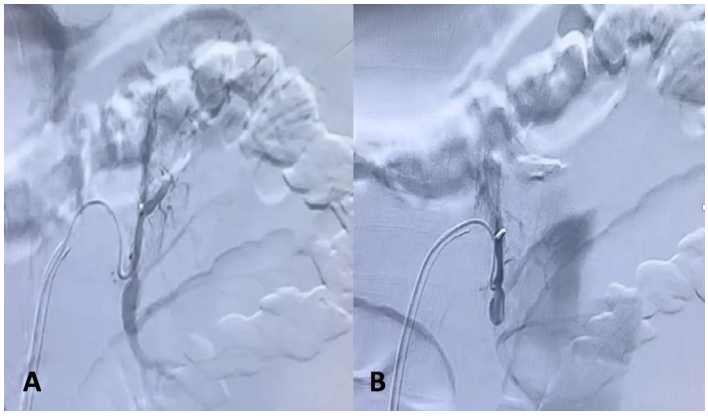

Figure 3. A: Pre-embolization angiography and B: Post-embolization angiography demonstrating successful occlusion of the bleeding arterial branch using a VortX coil

The patient showed rapid clinical improvement. Hemoglobin increased to 10.8 g/dL post-procedure and reached 13.8 g/dL at five-month follow-up. Renal function remained stable (creatinine 1.18 mg/dL), proteinuria resolved, and blood pressure became well controlled at 120–130/80–90 mmHg with reduced antihypertensive therapy (ramipril 2.5 mg daily).

Discussion

Renal artery aneurysm (RAA) represents a unique entity within renovascular disease, functioning both as a consequence of long-standing hypertension and as a potential contributor to secondary hypertension, particularly in young patients. Chronic elevation of intraluminal pressure promotes vascular remodeling and weakening of the arterial wall, predisposing to aneurysm formation.[1,3]

In this patient, hypertension was likely influenced by intrarenal hemodynamic disturbances leading to activation of the renin–angiotensin–aldosterone system (RAAS). Turbulent blood flow or distal microvascular ischemia may stimulate renin release from the juxtaglomerular apparatus, resulting in increased angiotensin II and aldosterone levels and contributing to blood pressure dysregulation.[3] The marked reduction in blood pressure from 154/110 mmHg to 120–130/80–90 mmHg following aneurysm exclusion provides strong clinical evidence of a reversible renovascular component. This observation suggests that the aneurysm played a significant role in blood pressure dysregulation.[6,7]

An important clinical consideration is whether the patient's hypertension was purely essential or secondary in nature. In this case, a systematic evaluation for secondary causes was undertaken. Fibromuscular dysplasia was considered unlikely due to the absence of characteristic imaging findings, including multifocal stenosis or a "string-of-beads" appearance on computed tomography angiography.[4,5] There was also no history suggestive of trauma, infection, or systemic vasculitis, making these alternative etiologies less likely.

In addition, no clinical features strongly suggested common endocrine causes of secondary hypertension, such as primary aldosteronism or pheochromocytoma, although a

complete hormonal workup was not performed. Notably, the significant improvement in blood pressure and reduced antihypertensive requirement following endovascular intervention provides ex juvantibus evidence supporting a predominant renovascular mechanism.[3,6,7]

From a nephrological perspective, the initial mild proteinuria likely reflected functional glomerular injury due to elevated intraglomerular pressure in the setting of severe hypertension. The complete resolution of proteinuria after intervention suggests that renal damage had not yet progressed to irreversible structural changes, highlighting the importance of timely management.

The clinical presentation of ruptured RAA may be subtle despite significant hemorrhage, as demonstrated in this case, where the patient remained hemodynamically stable despite severe anemia and a large perirenal hematoma.[8,9] This underscores the importance of maintaining a high index of suspicion in young patients presenting with acute flank pain and uncontrolled hypertension.

Advances in endovascular therapy have shifted the management paradigm of RAA. Compared with open surgical repair, endovascular approaches offer lower procedural morbidity, shorter hospital stay, and better preservation of renal function, while surgical reconstruction remains a well-established option with favorable long-term outcomes in selected cases.[10–14] Rundback type I aneurysms, as observed in this case, are particularly amenable to coil embolization with favorable outcomes.[12,15] In this patient, selective coil embolization successfully excluded the aneurysm while preserving renal perfusion, which is crucial for renal salvage in a young individual. The stability of serum creatinine throughout follow-up further supports the effectiveness of this minimally invasive approach in preventing significant nephron loss.

Conclusion

This case highlights the importance of recognizing renal artery aneurysm as both a consequence and a potential cause of hypertension. In young patients with uncontrolled or resistant hypertension, renovascular abnormalities should be actively considered. The marked improvement in blood pressure and resolution of proteinuria following endovascular intervention emphasize the presence of a reversible renovascular mechanism. Early diagnosis and timely minimally invasive management are essential to prevent life-threatening complications and preserve renal function.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: AASUK. Design: AASUK. Control/supervision: LS, RS. Data collection/ processing: AASUK. Analysis/interpretation: AASUK. Literature review: AASUK. Writing the article: AASUK. Critical review: LS, RS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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