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## Editorial



## Original Article



## Case Report



## Review Article



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**Editorial**

# Kidney Injury Molecule-1 (KIM-1): Biomarker of Tubular Injury and Predictor of Kidney Disease Progression

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To date, the definition and classification of Chronic Kidney Disease (CKD) remain based on two primary criteria: a decline in the estimated Glomerular Filtration Rate (eGFR) derived from serum creatinine, and increased urinary albumin excretion (urine albumin-to-creatinine ratio/ UACR). Serum creatinine is a biomarker of filtration function whose levels rise only after significant renal function loss—when up to 50% of the kidney has sustained irreversible damage.[1] In other words, a CKD diagnosis is established only after extensive tubulointerstitial fibrosis and glomerulosclerosis have already occurred (the "blind spot" phenomenon). Interstitial fibrosis and tubular atrophy (IFTA) serve as the histological markers with the strongest predictive value for progressive loss of kidney function, regardless of the disease's primary etiology.[2] This situation leads to delayed early intervention in both Acute Kidney Injury (AKI) and CKD. "As eGFR is dipping, the clock is ticking."

Consequently, there is a need to shift focus toward the tubulointerstitial compartment, particularly the proximal tubule, a highly metabolically active structure that is consequently very vulnerable to ischemia, toxins, and oxidative stress. Among the various tubular biomarkers, Kidney Injury Molecule-1 (KIM-1) has emerged as the most promising diagnostic and prognostic marker.[3]

## KIM-1 in AKI and CKD

KIM-1, also known as Hepatitis A virus cellular receptor-1 (HAVCR-1) or T-cell immunoglobulin and mucin-domain containing-1 (TIM-1), is a type I transmembrane glycoprotein that is virtually unexpressed in proximal tubule cells under healthy renal conditions. However, following injury caused by ischemia or nephrotoxicity, KIM-1 gene expression increases rapidly.[4] Urinary KIM-1 levels correlate strongly with tissue levels and, consequently, with the extent of renal tissue damage. KIM-1 not only serves as an early biomarker for AKI but also holds the potential to predict long-term renal outcomes.[5]

- **In Acute Kidney Injury (AKI):** Detection of uKIM-1 (urine) and pKIM-1 (plasma) offers diagnostic performance for early detection that is far superior to serum creatinine. Recent meta-analyses indicate that uKIM-1 and pKIM-1 exhibit high sensitivity and specificity (AUC ~0.81) for detecting AKI in post-cardiac surgery patients or in cases involving ischemia or drug-induced kidney injury.[6]
- **In Chronic Kidney Disease (CKD):** In CKD, elevated KIM-1 levels reflect ongoing active tubular injury or subclinical tubular stress that goes undetected by

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eGFR. KIM-1 provides a true picture of the burden of interstitial damage in diabetic nephropathy, hypertensive nephropathy, and glomerulonephritis.[7]

However, in contrast to previous studies, in this edition of InaKidney, Sari et al. demonstrate that urinary KIM-1 levels have low diagnostic value for AKI in patients with sepsis.[8] This discrepancy in results may indicate pathophysiological differences dependent on the underlying cause of the AKI. Indeed, sepsis-associated AKI is a complex and heterogeneous condition involving various mechanisms, such as microcirculatory dysfunction, systemic inflammatory responses, and cellular metabolic disturbances.[9] Another potential influencing factor is the timing of sample collection relative to the onset of injury; urinary KIM-1 levels can detect AKI in sepsis patients as early as two hours post-injury.[10] Limitations in study design may also play a role, necessitating more careful consideration and rigorous examination.[7]

**KIM-1: A Predictor of Progression and Adverse Renal Outcomes**

The most crucial role of KIM-1, distinguishing it from classic biomarkers, is its ability to predict long-term renal outcomes. Persistent elevation of KIM-1 expression following AKI is associated with disease progression and contributes to inflammatory damage and interstitial fibrosis in the kidney through extracellular matrix (ECM) deposition and epithelial-to-mesenchymal transition (EMT).[11,12]

Long-term clinical cohort studies confirm that baseline KIM-1 levels (in both plasma and urine) independently correlate with rapid eGFR decline and the risk of progression to end-stage renal disease (ESRD) and cardiovascular mortality in patients with diabetic kidney disease (DKD).[13] Thus, KIM-1 serves as a potent biomarker for the non-invasive assessment of renal tubular injury and disease activity during the progression of CKD, as well as for monitoring therapeutic response. By monitoring KIM-1 levels, clinicians can assess the severity of kidney injury, identify patients at risk of developing CKD, and implement timely interventions.[7]

**Integration of Tubular Injury and Glomerular Filtration Biomarkers: Subclinical CKD and Its Implications**

This new paradigm integrates two complementary biological compartments of the kidney: biomarkers of proximal tubular injury and biomarkers of precise or early glomerular filtration. This shift drives a proposal to align the classification of CKD using a complementary matrix (function versus structure). Patients with normal eGFR but positive biomarkers for tubular injury (e.g., KIM-1) are categorized as having subclinical CKD, molecular CKD, or pre-CKD. Patients with eGFR < 60 ml/min and positive biomarkers are classified as having progressive CKD (characterized by ongoing tissue damage), whereas those with negative biomarkers are classified as having inactive or stable CKD (characterized by the loss of nephron mass).

However, the utility of KIM-1 extends beyond mere risk stratification; the biomarker also serves as a surrogate marker to assess the efficacy of novel nephroprotective therapies. Consequently, patients with subclinical CKD can receive optimal pharmacological interventions, such as SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists (nsMRAs), or anti-inflammatory/anti-fibrotic agents—to prevent permanent loss of nephron mass.

Shifting the paradigm of CKD management through the use of early biomarkers for tubular injury and glomerular filtration represents an urgent clinical need. Integrating KIM-1 and other tubular biomarkers with early glomerular filtration biomarkers into daily clinical practice enables nephrologists to transition from reactive diagnosis to proactive, precision medical management, moving from an era of merely "slowing the decline of kidney function" to one of "preventing organ failure at an early stage."

## Declarations

### Competing interest

The author declares no conflict of interest.

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Original Article

# Diagnostic Value of Urinary Kidney Injury Molecule-1 in Diagnosis 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 serum creatinine, this condition possibly makes therapy delayed. Kidney Injury Molecule-1 (KIM-1) is a a type 1 transmembrane protein with immunoglobulin and mucin domains, which is expressed increased in the proximal tubules of the kidney. Elevated urinary KIM-1 levels are an indicator of AKI. However, previous studies have shown varying results.

***Objective:*** This study aims to determine early diagnostic biomarkers for the presence of 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 94 sepsis patients; only 22,34% (n=21) of them experienced AKI. Serum creatinine levels at admission and within 48 hours of hospitalization were 0,7 (IQR 0,2-1,6) mg/dl and 0,8 (IQR 0,3-2,2m) mg/dl. A urinary KIM-1 level at admission ≥11,74 ng/mL had a sensitivity of 44,68%, a specificity of 59,57%, a positive predictive value of 52,5%, a negative predictive value of 51,85%, and an accuracy of 52,12% in early diagnosis of AKI in sepsis.

***Conclusion:*** Urinary Klevel has poor diagnostic value in the diagnosis of AKI in sepsis.

***Keywords:*** Sepsis, Kidney injury molecule-1, AKI.

## Introduction

Acute kidney injury (AKI) is part of the spectrum of acute kidney disease (AKD) characterized by decreased kidney function and persistent dysfunction associated with functional loss leading to chronic kidney disease (CKD). Acute kidney injury (AKI) is defined as an increase in serum creatinine of ≥ 0.3 mg/dl within 48 hours or an increase in serum creatinine of ≥ 1.5 times the baseline estimated within the

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past week or a decrease in urine output of < 0.5 ml/kg/hour within 6 hours.[1]

The global burden of mortality due to AKI far exceeds the global burden of mortality due to breast cancer, heart failure, or diabetes, with mortality rates remaining high for the past 50 years. Acute kidney injury is a major and significant problem frequently encountered in intensive care units (ICUs). Worldwide, AKI is reported to occur in 20% or even more than 50% of ICU patients. A study by Hoste et al. found that the incidence of AKI in 1,802 ICUs from 33 countries was 57.3%. AKI patients are dominated by sepsis patients, at about 53%.[1–3]

The use of serum creatinine as the basis for AKI diagnosis also has several limitations. Structural kidney injury without a corresponding increase in serum creatinine may occur in conditions such as sepsis due to hemodilution or sarcopenia in geriatric patients, leading to a "failure to rise" in creatinine and delayed treatment. Conversely, conditions without actual kidney injury but accompanied by elevated serum creatinine levels, such as prerenal azotemia, liver cirrhosis, or the early use of diuretics and antihypertensive medications, may result in inappropriate treatment. Therefore, serum creatinine-based diagnosis has low sensitivity and specificity.[4,5]

Kidney injury molecule-1 was first identified by Ichimura et al in 1998. Kidney injury molecule-1 is a type 1 transmembrane protein with immunoglobulin and mucin domains, upregulated in the proximal tubule of the kidney. Normally, this structure is found within cells. When proximal tubule damage occurs, it is released into the extracellular space. This is the basis for KIM-1's use as a diagnostic marker for AKI.[6]

The 28th Acute Disease Quality Initiative (ADQI) consensus recommends the use of additional biomarkers in establishing the diagnosis of AKI in sepsis. The goal is early detection and appropriate management before permanent complications occur. A study by Xie et al. (2021) found that urinary KIM-1 can detect AKI in sepsis patients earlier than several other biomarkers, with urinary KIM-1 increasing within the first 2 hours after kidney injury. Furthermore, a study by Shaker et al. (2023) found that urinary KIM-1 levels were significantly higher in AKI patients with sepsis earlier than serum creatinine. Serum creatinine increased within 24 or even 48 hours after kidney damage in sepsis patients. Another study by Juwono et al. (2024) found that urinary KIM-1 could be a potential marker for early diagnosis of AKI. Urinary Kidney Injury Molecule-1 appears within 6-12 hours after kidney damage, even before serum creatinine increases. Another study conducted by Mohamed et al (2024) also concluded that urinary KIM-1 can detect AKI in sepsis patients earlier than serum creatinine, so that patients can receive faster treatment before it develops into chronic kidney disease.[7–10]

## Methods

### Design and participants

This study is a diagnostic test using a cross-sectional approach conducted in inpatients of Dr. M. Djamil Central General Hospital, Padang. Samples were collected from October 2025 to February 2026. First, we determined the inclusion and exclusion criteria, then urine and 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 94 people was obtained. The subjects taken as samples were subjects who met the inclusion criteria and did not meet the exclusion criteria. The inclusion criteria were sepsis patients with normal serum creatinine levels. Patients with a history of chronic kidney disease (CKD), anuria, lupus nephritis, nephrotic syndrome, nephrolithiasis, polycystic kidney disease, renal cell carcinoma, diabetic nephropathy, and urinary tract infection were excluded from the study.

Testing of Urinary KIM-1 was carried out using the ELISA (Enzyme-linked Immunoassay) method using the YL Biont reagent in the Biomedical Laboratory of the

Medicine Faculty of Andalas University, Padang. An elevated serum creatinine 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 urinary KIM-1 level was calculated by the Youden Index in the ROC. After that, we assessed diagnostic performance by calculating sensitivity, specificity, negative predictive value, positive predictive value, and accuracy using Table 2 x 2.

## Results

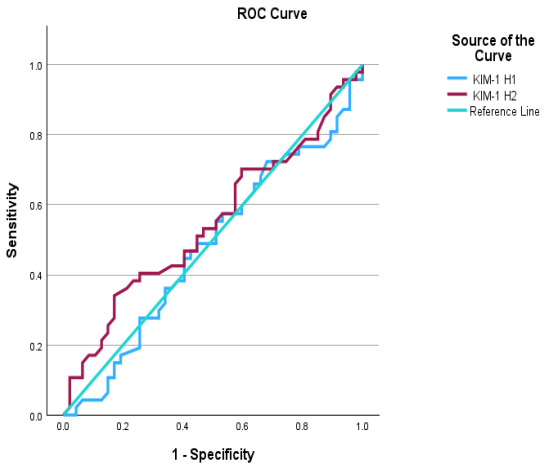
### Patient characteristic

This study involved 94 patients with a sepsis diagnosis while admitted. The average age of the sample is 65,5 (IQR 48.8 – 70.0) years. The proportion of the geriatric and nongeriatric subgroups is 67% and 33%, respectively. In this study, female patients with suspected sepsis-associated AKI were more prevalent than males, accounting for 60.6% and 39.4%, respectively. A total of 88.3% of patients were treated in the High Care Unit (HCU), while 11.7% were admitted to the Intensive Care Unit (ICU). The comorbidities identified among sepsis patients included hypertension (67%), diabetes mellitus (33%), chronic heart disease and stroke (36.2%), and malignancy (8.5%).

Median SOFA score at admission is 5. The primary source of infection is pneumonia 89,3%, skin and soft tissue infection (SSTI) 21,3%, and other infection 6,4%. Almost 91.9% were unifocal infections. Laboratory findings demonstrated a median hemoglobin level of 10.3 g/dL (IQR 3.9–16.7 g/dL). The median lactate level was 1.8 mmol/L (IQR 0.5–8.3 mmol/L), while the median albumin level was 2.6 g/dL (IQR 1.3–4.1 g/dL). The median serum creatinine level on the first day of hospitalization was 0.7 mg/dL (IQR 0.2–1.6 mg/dL), increasing to 0.8 mg/dL (IQR 0.3–2.2 mg/dL) on the second day. Median urinary KIM-1 levels on admission were 10.6 ng/mL (IQR 1.2–19.5 ng/mL), while on the second day of hospitalization the median level increased to 11.5 ng/mL (IQR 1.5–19.2 ng/mL).

### Diagnostic Value of Urinary KIM-1

First, the optimal cut-off value of urinary KIM-1 level is calculated by the Youden index. A urinary KIM-1 level at admission> 11.74 ng/mL had a sensitivity of 44,68%, specificity of 59,57%, positive predictive value of 52,5%, negative predictive value of 51,85%, and accuracy of 52,12% in early detection of AKI in sepsis. We also calculated the optimal cut-off within 48 hours of hospitalization ($H_2$). The result is ≥15,41 ng/mL with AUC 0,547 (CI 95%; 0,430-0,665) and Youden Index 0,170. In this study, we found 21 AKI and 19 non-AKI based on KDIGO criteria. The ROC and diagnostic performances from this study can be seen in Picture 1 and the table below.




**Picture 1.** Receiver Operation Curve (ROC)

**Table 1.** Characteristics of Respondents

| Variable n = 94 | Value n = 94 |
|---|---|
| **Age (years), median (Min-Max)** | 65,5 (18–101) |
| **Age group, n (%)** | |
| < 60 years | 31 (33) |
| ≥ 60 years | 63 (67) |
| **Sex, n (%)** | |
| Male | 37 (39,4) |
| Female | 57 (60,6) |
| **Type of care unit, n (%)** | |
| ICU | 11 (11,7) |
| HCU | 83 (88,3) |
| **Comorbidities, n (%)** | |
| Diabetes mellitus | 31 (33) |
| Hypertension | 63 (67) |
| Stroke/heart disease[4] | 34 (36,2) |
| Malignancy | 8 (8,5) |
| **Number of comorbidities, n (%)** | |
| One comorbidity | 58 (61,7) |
| Multimorbidity | 36 (38,2) |
| **SOFA score, median (Min-Max)** | 5 (3–12) |
| **Source of infection, n (%)** | |
| Pneumonia | 84 (89,3) |
| Skin and soft tissue infection | 20 (21,3) |
| Other infections | 6 (6,4) |
| **Focality of infection, n (%)** | |
| Unifocal | 74 (73,4) |
| Multifocal | 20 (26,6) |

**Table 2.** Laboratory Parameters

| Variable n = 94 | Value n = 94 |
|---|---|
| **Laboratory parameters, median (Min-Max)** | |
| Hb (g/dL) | 10,3 (3,9–16,7) |
| Lactate (mmol/L) | 1,8 (0,5–8,3) |
| Albumin (g/dL) | 2,6 (1,3–4,1) |
| Creatinine, Day 1 (mg/dL) | 0,7 (0,2–1,6) |
| Creatinine, Day 2 (mg/dL) | 0,8 (0,3–2,2) |
| Urinary KIM-1, Day 1 (ng/mL) | 10,6 (1,2–19,5) |
| Urinary KIM-1, Day 2 (ng/mL) | 11,5 (1,5–19,2) |

**Table 3.** Diagnostic Performance of Urinary KIM-1 to Diagnose Sepsis-Associated AKI

| Day of Test | KIM-1 (ng/mL) | AKI KDIGO | | Sensitivity | Specivicity | NPV | PPV | Acuration |
|---|---|---|---|---|---|---|---|---|
| | | Yes | No | | | | | |
| at Admission ($H_1$) | ≥11,74 | 21 | 9 | 44,68% | 59,57% | 52,5% | 51,85% | 52,12 % |
| | <11,74 | 26 | 28 | | | | | |
| 48 hours in hospitalization ($H_2$) | ≥15,41 | 16 | 8 | 34,04% | 82,9% | 66,6% | 55,7% | 58,51% |
| | <15,41 | 31 | 39 | | | | | |

## Discussion

In this study, we reported that urinary KIM-1 has poor diagnostic performance for early detection of AKI in sepsis patients. While serum creatinine was normal at admission, elevated urinary KIM-1 levels of more than 11,74 ng/mL resulted in a sensitivity of 44.68%, specificity of 59.57%, negative predictive value 52,5%, positive predictive value 51,85% and accuracy of 52.12% (AUC 0,478).

A study conducted by Matarneh et al (2025) involving 35 studies covering >6000 critically ill patients evaluated three biomarkers for early detection of AKI, namely: NGAL, KIM-1, and TIMP-2IGFBP7. Kidney injury molecule-1 showed lower overall diagnostic accuracy. However, KIM-1 may offer clinical value in identifying patients with ongoing tubular injury or in risk stratification during the subacute phase. Kidney injury molecule-1 is a transmembrane protein released by injured proximal tubular cells and is usually measured in urine. When compared with NGAL and TIMP-2IGFBP7, KIM-1 reflects more persistent kidney injury. The AUC values in this review ranged from 0.62 to 0.74. The sensitivity and specificity of KIM-1 were more moderate in this study, namely 70-8% and 60-85%, respectively. Several studies have shown its potential to differentiate transient from persistent AKI and to predict long-term renal recovery. Therefore, KIM-1 may be more useful for AKI prognosis and phenotype than for early diagnosis. Several included studies showed that KIM-1 levels remained elevated after 48 hours, supporting its role in detecting ongoing and persistent injury. This is in line with the finding that KIM-1 may be more useful for long-term kidney damage than for early-onset AKI.[11,12]

A study by Puspitasari et al. (2025) found significant differences in urinary KIM-1, IL-18, and IGFBP-7 levels between sepsis patients with and without AKI. The cutoff point for urinary KIM-1 levels in sepsis with and without AKI was 1.666 ng/ml, with a sensitivity of 82.5%, a specificity of 82.2%, and a relative risk (RR) [95% confidence interval (CI)] of 6.866 (95% CI, 3.329–14.165). The cutoff point for urinary IL-18 levels was 3.868 ng/ml, with a sensitivity of 92.50%, a specificity of 91.78%, and an RR of 20.078 (95% CI, 6.593–61.142). The cutoff point for urinary IGFBP-7 levels was ≥0.906 ng/ml with a sensitivity of 75.00%, specificity of 75.34%, and RR of 4.063 (95% CI, 2.206–7.483). This study conducted three sampling sessions: on the first, third, and seventh days. The first day was when the patient was first admitted or diagnosed with sepsis, followed by the third and seventh days. The study sample consisted of 56 individuals, with comorbid diabetes mellitus being the most common, at 23.21%. Differences in population characteristics, including the most common comorbidities and the number of sampling days, could be factors contributing to the differences in study results. In this study, KIM-1 demonstrated a good AUC on the third day of sampling. This suggests that KIM-1 cannot be used in this population, specifically sepsis patients, despite positive results in several previous studies.[13]

According to a study by Zhang and Liu (2025), KIM-1 is normally absent in healthy kidneys, whereas acute kidney injury results in an initial increase in KIM-1 and exhibits anti-inflammatory and protective functions by facilitating the clearance of damaged and apoptotic cells. However, sustained increased KIM-1 expression after AKI is associated with the development of CKD.[14]

A study conducted by Yang et al (2025) stated that urinary KIM-1 can differentiate between transient AKI and persistent AKI. In addition, KIM-1 can also be used to predict long-term kidney damage with an AUC of 0.703, a sensitivity of 78.4%, and a specificity of 60.8%, and KIM-1 levels > 2.37 ng/mg are said to be associated with a poor prognosis. A recent study also stated that in diagnosing AKI, urinary KIM-1 has a sensitivity of 74% and a specificity of 84% with an AUC of 0.622. This study also stated that the sensitivity, specificity, and AUC of urinary KIM-1 in diagnosing contrast-induced AKI (CI-AKI) were 84%, 78%, and 0.88, respectively.[15]

In this study, it was found that the AUC value of urinary KIM-1 in detecting AKI in sepsis patients still showed less than optimal performance. These results indicate that the discriminatory ability of KIM-1 in differentiating AKI and non-AKI patients in this study population is relatively limited. This finding is likely influenced by the heterogeneity of AKI pathophysiology in sepsis. Based on a study by Osterman et al (2018), AKI in sepsis is a complex and heterogeneous condition, involving various mechanisms such as microcirculatory dysfunction, systemic inflammatory response, and cellular metabolic disorders. This condition results in various AKI phenotypes, ranging from hemodynamic disturbances without structural damage to overt tubular injury.[16]

## Conclusion

Urinary KIM-1 level tests have poor diagnostic performance for early detection of sepsis-associated AKI.

## Limitations of the Study

This study was conducted at a single healthcare center. It also did not evaluate the influence of confounding factors such as comorbidities or compare KIM-1 with other AKI biomarkers.

## 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.10.1/454/2025.

### Competing interests

There are no conflicts of interest in writing this article.

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### Author's Contribution

Idea/concept: PAS. Design: PAS. Control/supervision: DP, HH, DV. Data collection/ processing: PAS, DV, NN, FF, DE, AWM. Analysis/interpretation: PAS, DP, HH, DV. Literature review: -. Writing the article: PAS. Critical review: DP, HH, DV, DV, NN, FF, DE, 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

# Differences in Neutrophil-to-Lymphocyte Ratio, Hemoglobin, and Ferritin Between Arteriovenous Shunt and Hemodialysis Catheter in Maintenance Hemodialysis Patients

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**ABSTRACT**

***Background:*** Vascular access type may influence systemic inflammation and hematologic profiles in patients undergoing maintenance hemodialysis.
***Objective:*** This study aimed to compare neutrophil-to-lymphocyte ratio, hemoglobin, and ferritin levels between patients using arteriovenous fistulas and hemodialysis catheters.
***Methods:*** This cross-sectional analytical study included 128 patients undergoing maintenance hemodialysis, consisting of 85 patients with arteriovenous fistulas and 43 with hemodialysis catheters. Neutrophil-to-lymphocyte ratio and ferritin levels were compared using the Mann–Whitney U test, whereas hemoglobin levels were analyzed using the independent-samples t-test. Multiple linear regression was performed to assess the independent association between vascular access type and each laboratory parameter after adjustment for potential confounders.
***Results:*** Patients using hemodialysis catheters had a significantly higher neutrophil-to-lymphocyte ratio than those with arteriovenous fistulas (median 4.92 vs. 4.13; p=0.049). Hemoglobin levels were also higher in the catheter group (8.82 ± 1.57 vs. 8.19 ± 1.62 g/dL; p=0.038). Ferritin levels were numerically higher among catheter users but were not significantly different in unadjusted analysis (p=0.154). After multivariable adjustment, hemodialysis catheter use remained independently associated with higher neutrophil-to-lymphocyte ratio, hemoglobin, and ferritin levels.
***Conclusion:*** Hemodialysis catheter use was associated with higher inflammatory and hematologic biomarker levels compared with arteriovenous fistula use among patients undergoing maintenance hemodialysis.
***Keywords:*** chronic kidney disease; hemodialysis; arteriovenous fistula; hemodialysis catheter; neutrophil-to-lymphocyte ratio; hemoglobin; ferritin.

## Introduction

Chronic kidney disease (CKD) is a major global health challenge, affecting approximately 788 million adults worldwide and ranking among the leading causes of mortality and disability.[1] The increasing prevalence of end-stage kidney disease has resulted in a growing number of patients requiring maintenance hemodialysis

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(HD), despite substantial advances in kidney replacement therapy.[2] Patients receiving maintenance HD continue to experience high rates of cardiovascular events, infection, hospitalization, and premature mortality, with chronic systemic inflammation recognized as one of the principal mechanisms contributing to these adverse outcomes.[2–4]

Vascular access is fundamental to delivering effective maintenance HD. Current clinical guidelines recommend an arteriovenous fistula (AVF) as the preferred long-term vascular access because of its superior patency, lower infection risk, and lower incidence of access-related complications than central venous catheters (CVCs).[2,5] Nevertheless, CVCs remain widely used for urgent dialysis initiation, failure of permanent vascular access, or when AVF creation is not feasible.[2] Prolonged catheter use has been associated with biofilm formation, catheter-related bloodstream infection, thrombosis, endothelial injury, and persistent activation of the inflammatory response, potentially contributing to poorer clinical outcomes than AVF.[6–8]

Inflammation is highly prevalent among patients undergoing maintenance HD and contributes to anemia, malnutrition, accelerated atherosclerosis, cardiovascular disease, and increased mortality.[3,4] Conventional inflammatory biomarkers, including C-reactive protein (CRP) and interleukin-6 (IL-6), are well-established indicators of systemic inflammation but are not routinely available in many clinical settings because of their cost and limited accessibility.[9] Consequently, increasing attention has been directed toward inexpensive inflammatory biomarkers that can be derived from routine laboratory investigations. The neutrophil-to-lymphocyte ratio (NLR), calculated from a complete blood count, has emerged as a reliable marker of systemic inflammation and has been associated with adverse cardiovascular outcomes and all-cause mortality in patients receiving maintenance HD.[10–12] Hemoglobin and ferritin are also routinely monitored in HD patients to evaluate anemia management and iron status. Beyond its role as an iron-storage protein, ferritin acts as an acute-phase reactant, and chronic inflammation contributes to impaired erythropoiesis by disrupting iron metabolism and increasing hepcidin production.[13–15]

Several studies have demonstrated that catheter-based vascular access is associated with greater inflammatory activity than AVF. Crespo-Montero et al. reported higher inflammatory marker levels among patients with tunneled hemodialysis catheters than those with AVF. In contrast, Goldstein et al. observed increased inflammation even in the absence of catheter-related infection.[6,16] More recently, Yousefi et al. evaluated the association between vascular access type and malnutrition-inflammation-atherosclerosis syndrome but found no significant differences in ferritin concentrations between catheter and fistula users.[17] Although previous studies have examined selected inflammatory markers, evidence simultaneously evaluating NLR, hemoglobin, and ferritin according to vascular access type remains scarce. In addition, the independent association between vascular access type and these routinely available laboratory parameters has not been adequately investigated after adjustment for potential confounding factors.

We hypothesized that vascular access type is associated with differences in inflammatory and hematologic biomarkers among patients undergoing maintenance hemodialysis. Therefore, this study aimed to compare NLR, hemoglobin, and ferritin levels according to vascular access type among patients undergoing maintenance hemodialysis and to evaluate whether vascular access type was independently associated with these laboratory parameters after adjustment for relevant clinical confounders.

## Methods

### Study design and participants

A hospital-based cross-sectional analytical study was conducted at the hemodialysis unit of a tertiary referral hospital in Indonesia. The study included all eligible patients undergoing maintenance hemodialysis during May 2026. A total sampling approach was employed, whereby all patients who met the eligibility criteria during the study period were included.

Adult patients undergoing maintenance hemodialysis through either an arteriovenous fistula (AVF) or a hemodialysis catheter were eligible for inclusion. Patients with active infection, malignancy, autoimmune disease, hematological disorders, recent surgery or trauma, acute bleeding, or incomplete medical records were excluded because these conditions could influence inflammatory and hematologic biomarkers.

**Data collection**

Demographic and clinical data were obtained retrospectively from patients' medical records. Variables collected included age, sex, body mass index (BMI), smoking status, duration of hemodialysis, vascular access type, comorbidities, and medication use. Data regarding hypertension, diabetes mellitus, dyslipidemia, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy, statin use, erythropoiesis-stimulating agent administration, and iron supplementation were also recorded.

**Laboratory measurements**

Laboratory data were obtained from routine blood examinations performed before the scheduled hemodialysis session. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Hemoglobin concentration (g/dL) and serum ferritin level (ng/mL) were retrieved from the corresponding laboratory records.

**Outcome measures**

The primary exposure variable was vascular access type, categorized as an arteriovenous fistula (AVF) or a hemodialysis catheter. The primary outcome measures were neutrophil-to-lymphocyte ratio, hemoglobin concentration, and serum ferritin level.

**Statistical analysis**

Data analysis was performed using IBM SPSS Statistics version 27.0. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median (interquartile range [IQR]). Categorical variables are expressed as frequencies and percentages.

Baseline characteristics were compared using the independent-samples t-test or the Mann-Whitney U test for continuous variables, as appropriate, and the chi-square test or Fisher's exact test for categorical variables.

Differences in NLR and ferritin levels between vascular access groups were analyzed using the Mann-Whitney U test, whereas hemoglobin levels were compared using the independent-samples t-test. Variables considered clinically relevant or showing a p value $<0.25$ in the bivariate analysis were entered into multiple linear regression models to evaluate the independent association between vascular access type and each outcome after adjustment for potential confounding variables. A two-sided p value $<0.05$ was considered statistically significant.

**Ethical approval**

This study was approved by the institutional Health Research Ethics Committee.

## Results

**Participant characteristics**

A total of 128 patients undergoing maintenance hemodialysis were included in this study, comprising 85 (66.4%) patients with an arteriovenous fistula (AVF) and 43 (33.6%) with a hemodialysis catheter.

Baseline demographic and clinical characteristics according to vascular access type are presented in Table 1. The two groups were comparable in most baseline characteristics. Significant differences were observed in hypertension, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) use, and statin use between the AVF and hemodialysis catheter groups.

**Table 1.** Baseline characteristics of patients according to vascular access type

| Variable | Total (N = 128) | AVF (n = 85) | HD catheter (n = 43) | p value |
|---|---|---|---|---|
| **Demographic and clinical characteristics** | | | | |
| Age (years) | 52.50 (19.00-96.00) | 54.00 (22.00-96.00) | 49.00 (19.00-83.00) | 0.419 |
| Sex, n (%) | | | | 0.286 |
| Female | 60 (46.9%) | 37 (43.5%) | 23 (53.5%) | |
| Male | 68 (53.1%) | 48 (56.5%) | 20 (46.5%) | |
| HD frequency, n (%) | | | | 0.134 |
| 2 times/week | 80 (62.5%) | 57 (67.1%) | 23 (53.5%) | |
| 1 time/week | 48 (37.5%) | 28 (32.9%) | 20 (46.5%) | |
| Duration of HD (months) | 16.00 (4.00-159.00) | 18.00 (4.00-121.00) | 11.00 (4.00-159.00) | 0.626 |
| Access duration (months) | 11.50 (1.00-134.00) | 15.00 (1.00-123.00) | 7.00 (1.00-134.00) | 0.105 |
| Etiology of CKD, n (%) | | | | 0.117 |
| Diabetic nephropathy | 35 (27.3%) | 26 (30.6%) | 9 (20.9%) | |
| Hypertensive nephropathy | 86 (67.2%) | 57 (67.1%) | 29 (67.4%) | |
| Lupus nephritis | 2 (1.6%) | 1 (1.2%) | 1 (2.3%) | |
| Unknown etiology | 2 (1.6%) | 1 (1.2%) | 1 (2.3%) | |
| Obstructive uropathy | 3 (2.3%) | 0 (0.0%) | 3 (7.0%) | |
| **Comorbidities** | | | | |
| Hypertension, n (%) | | | | 0.021* |
| Yes | 113 (88.3%) | 79 (92.9%) | 34 (79.1%) | |
| No | 15 (11.7%) | 6 (7.1%) | 9 (20.9%) | |
| Diabetes mellitus, n (%) | | | | 0.325 |
| Yes | 40 (31.3%) | 29 (34.1%) | 11 (25.6%) | |
| No | 88 (68.8%) | 56 (65.9%) | 32 (74.4%) | |
| Heart failure, n (%) | | | | 0.082 |

| Variable | Total (N = 128) | AVF (n = 85) | HD catheter (n = 43) | p value |
|---|---|---|---|---|
| Yes | 46 (35.9%) | 35 (41.2%) | 11 (25.6%) | |
| No | 82 (64.1%) | 50 (58.8%) | 32 (74.4%) | |
| CAD/IHD, n (%) | | | | 0.717 |
| Yes | 8 (6.3%) | 6 (7.1%) | 2 (4.7%) | |
| No | 120 (93.8%) | 79 (92.9%) | 41 (95.3%) | |
| **Medication use** | | | | |
| ACEI/ARB, n (%) | | | | 0.015* |
| Yes | 97 (75.8%) | 70 (82.4%) | 27 (62.8%) | |
| No | 31 (24.2%) | 15 (17.6%) | 16 (37.2%) | |
| Statin, n (%) | | | | 0.046* |
| Yes | 28 (21.9%) | 23 (27.1%) | 5 (11.6%) | |
| No | 100 (78.1%) | 62 (72.9%) | 38 (88.4%) | |
| CCB, n (%) | | | | 0.128 |
| Yes | 83 (64.8%) | 59 (69.4%) | 24 (55.8%) | |
| No | 45 (35.2%) | 26 (30.6%) | 19 (44.2%) | |
| Diuretic, n (%) | | | | 0.546 |
| Yes | 82 (64.1%) | 56 (65.9%) | 26 (60.5%) | |
| No | 46 (35.9%) | 29 (34.1%) | 17 (39.5%) | |
| Beta blocker, n (%) | | | | 0.846 |
| Yes | 22 (17.2%) | 15 (17.6%) | 7 (16.3%) | |
| No | 106 (82.8%) | 70 (82.4%) | 36 (83.7%) | |
| Aspirin, n (%) | | | | 0.750 |
| Yes | 11 (8.6%) | 8 (9.4%) | 3 (7.0%) | |
| No | 117 (91.4%) | 77 (90.6%) | 40 (93.0%) | |
| ESA use within 4 weeks, n (%) | | | | 0.856 |

| Variable | Total (N = 128) | AVF (n = 85) | HD catheter (n = 43) | p value |
|---|---|---|---|---|
| Yes | 31 (24.2%) | 21 (24.7%) | 10 (23.3%) | |
| No | 97 (75.8%) | 64 (75.3%) | 33 (76.7%) | |
| Iron therapy within 4 weeks, n (%) | | | | 0.670 |
| Yes | 27 (21.1%) | 17 (20.0%) | 10 (23.3%) | |
| No | 101 (78.9%) | 68 (80.0%) | 33 (76.7%) | |

Note: Data are presented as median (minimum-maximum) for non-normally distributed continuous variables and as frequency (percentage) for categorical variables. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the Pearson chi-square test or Fisher's exact test, as appropriate. An asterisk (*) denotes statistical significance ($p < 0.05$).

**Comparison of neutrophil-to-lymphocyte ratio, hemoglobin, and ferritin levels**

Comparisons of neutrophil-to-lymphocyte ratio (NLR), hemoglobin, and ferritin levels between patients with different vascular access types are shown in Table 2. Patients using hemodialysis catheters had a significantly higher median NLR than those using AVFs (4.92 vs. 4.13, p = 0.049). Mean hemoglobin concentration was also significantly higher in the hemodialysis catheter group than in the AVF group (8.82 ± 1.57 vs. 8.19 ± 1.62 g/dL, p = 0.038). Ferritin levels were higher among patients with hemodialysis catheters; however, the difference was not statistically significant (p = 0.154).

**Table 2.** Comparison of study variables according to vascular access type

| Variable | Total (N = 128) | AVF (n = 85) | HD catheter (n = 43) | p value |
|---|---|---|---|---|
| NLR | 4.63 (0.02-55.18) | 4.13 (0.02-16.11) | 4.92 (1.28-55.18) | 0.049* |
| Hemoglobin (g/dL) | 8.40 ± 1.63 | 8.19 ± 1.62 | 8.82 ± 1.57 | 0.038* |
| Ferritin (ng/mL) | 756.00 (23.00-3000.00) | 754.00 (26.80-3000.00) | 826.00 (23.00-3000.00) | 0.154 |

Note: Hemoglobin level is presented as mean ± standard deviation (SD), whereas NLR and ferritin level are presented as median (minimum-maximum). Between-group comparisons were performed using the independent-samples t-test or the Mann-Whitney U test, as appropriate. An asterisk (*) indicates statistical significance (p < 0.05).

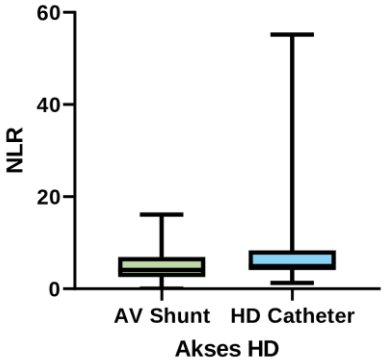


**Figure 1.** Box plot of neutrophil-to-lymphocyte ratio according to vascular access type

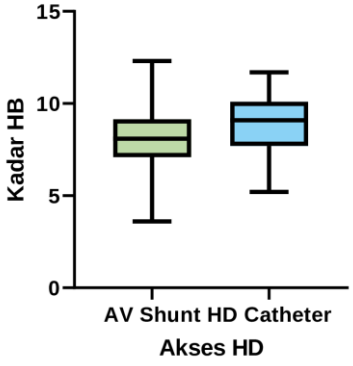


**Figure 2.** Box plot of hemoglobin levels according to vascular access type

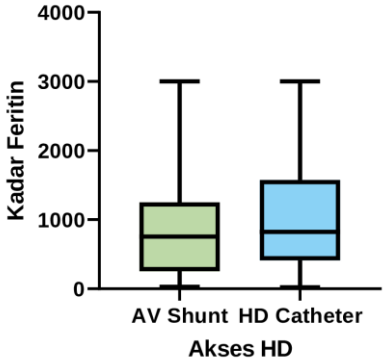


**Figure 3.** Box plot of ferritin levels according to vascular access type

**Multivariable analysis**

The associations between vascular access type and laboratory parameters after adjustment for hypertension, ACEI/ARB use, and statin use are presented in Tables 3-5. In the adjusted analyses, hemodialysis catheter use was significantly associated with higher NLR (B = 3.009, p = 0.020), higher hemoglobin concentration (B = 0.769, p = 0.016), and higher ferritin level (B = 307.050, p = 0.039).

**Table 3.** Multivariable linear regression analysis of factors associated with neutrophil-to-lymphocyte ratio

| Independent variable | Unstandardized coefficient (B) | 95% confidence interval | Standardized coefficient (β) | p value |
|---|---|---|---|---|
| | | Lower to upper | | |
| (Constant) | 1.233 | -5.424 to 7.890 | — | 0.715 |
| Hypertension | -1.531 | -5.289 to 2.228 | -0.072 | 0.422 |
| ACEI/ARB use | 4.438 | 1.583 to 7.292 | 0.279 | 0.003* |
| Statin use | -1.492 | -4.316 to 1.332 | -0.091 | 0.298 |
| Vascular access | 3.009 | 0.486 to 5.531 | 0.209 | 0.020* |

Note: An asterisk (*) indicates statistical significance at $p < 0.05$.

**Table 4.** Multivariable linear regression analysis of factors associated with hemoglobin

| Independent variable | Unstandardized coefficient (B) | 95% confidence interval | Standardized coefficient (β) | p value |
|---|---|---|---|---|
| | | Lower to upper | | |
| (Constant) | 8.804 | 7.159 to 10.449 | — | <0.005 |
| Hypertension | -0.379 | -1.307 to 0.550 | -0.075 | 0.421 |
| ACEI/ARB use | 0.011 | -0.695 to 0.716 | 0.003 | 0.976 |
| Statin use | -0.571 | -1.269 to 0.127 | -0.145 | 0.108 |
| Vascular access | 0.769 | 0.146 to 1.392 | 0.224 | 0.016* |

Note: An asterisk (*) indicates statistical significance at $p < 0.05$.

**Table 5.** Multivariable linear regression analysis of factors associated with ferritin levels

| Independent variable | Unstandardized coefficient (B) | 95% confidence interval | Standardized coefficient (β) | p value |
|---|---|---|---|---|
| | | Lower to upper | | |
| (Constant) | 577.886 | -190.539 to 1346.312 | — | 0.139 |
| Hypertension | -6.000 | -439.838 to 427.838 | -0.003 | 0.978 |
| ACEI/ARB use | 93.542 | -235.940 to 423.024 | 0.053 | 0.575 |
| Statin use | -111.866 | -437.842 to 214.109 | -0.062 | 0.498 |
| Vascular access | 307.050 | 15.921 to 598.179 | 0.193 | 0.039* |

Note: An asterisk (*) indicates statistical significance at $p < 0.05$.

## Discussion

The present study evaluated the association between vascular access type and inflammatory and hematologic biomarkers among patients undergoing maintenance hemodialysis. Patients using hemodialysis catheters had significantly higher neutrophil-to-lymphocyte ratio (NLR) and hemoglobin levels than those using arteriovenous fistulas (AVFs). Although ferritin levels did not differ significantly in the unadjusted analysis, multivariable regression demonstrated that vascular access type remained independently associated with ferritin levels after adjustment for hypertension, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) use, and statin therapy. These findings support our hypothesis that vascular access type is associated with differences in inflammatory and hematologic biomarkers in patients receiving maintenance hemodialysis.

NLR is increasingly recognized as a readily available marker of systemic inflammation in patients with chronic kidney disease and has been associated with cardiovascular events, hospitalization, and all-cause mortality.[10–12] In the present study, patients using hemodialysis catheters had significantly higher NLR than those with AVFs, consistent with previous reports suggesting that catheter-based vascular access is associated with a greater inflammatory burden. Crespo-Montero et al. reported higher inflammatory marker levels among patients with tunneled dialysis catheters than among those with AVFs, while Goldstein et al. demonstrated persistent inflammation associated with catheter use even in the absence of overt catheter-related infection.[6,16] Chronic endothelial injury, biofilm formation, repeated vascular manipulation, and subclinical inflammatory activation associated with prolonged catheter use have been proposed as mechanisms contributing to sustained systemic inflammation.[6–8] Collectively, these findings reinforce current recommendations favoring AVFs as the preferred vascular access whenever clinically feasible.[2,5]

An unexpected finding of this study was the significantly higher hemoglobin concentration among patients using hemodialysis catheters. Chronic inflammation is generally associated with anemia through impaired erythropoiesis, increased hepcidin production, and reduced iron availability.[13–15] Therefore, lower hemoglobin levels might have been anticipated in catheter users. Several explanations may account for the present findings. First, differences in erythropoiesis-stimulating agent administration, intravenous iron therapy, or transfusion history, which were not evaluated in detail, may have influenced hemoglobin concentrations. Second, variability in clinical characteristics and treatment strategies between vascular access groups may have contributed to this observation. Finally, the cross-sectional design captures laboratory values at a single time point and cannot account for longitudinal changes in anemia management. Consequently, although vascular access type remained independently associated with hemoglobin concentration after adjustment for selected

confounders, this finding should be interpreted cautiously and warrants confirmation in prospective studies.

Serum ferritin is routinely used to assess iron stores in patients receiving hemodialysis but also functions as an acute-phase reactant that increases during systemic inflammation.[13,14] In the present study, ferritin levels were numerically higher among catheter users, although the difference was not statistically significant in the unadjusted analysis. Interestingly, vascular access type became significantly associated with ferritin levels after multivariable adjustment, suggesting that confounding variables may have masked the relationship in the crude comparison. Similar findings have been reported by previous studies demonstrating that ferritin concentrations are influenced by both iron metabolism and inflammatory activity, limiting their specificity as an isolated marker of inflammation.[15,17] Therefore, ferritin should be interpreted in conjunction with other clinical and laboratory parameters when evaluating inflammatory status in patients undergoing maintenance hemodialysis.

The findings of this study have several clinical implications. Because NLR is inexpensive, readily available, and routinely derived from complete blood counts, it may serve as a practical adjunctive marker for identifying patients with increased inflammatory burden, particularly among those using hemodialysis catheters. Furthermore, the independent association between vascular access type and multiple laboratory parameters underscores the importance of optimizing vascular access whenever possible. Although vascular access selection should remain individualized according to patient characteristics and clinical feasibility, these findings provide additional evidence supporting the preferential use of AVFs in patients requiring long-term maintenance hemodialysis.[2,5]

This study has several strengths. It simultaneously evaluated inflammatory and hematologic biomarkers that are routinely measured in clinical practice and employed multivariable regression analysis to account for important clinical confounders.

## Conclusion

This study demonstrated that vascular access type was associated with differences in inflammatory and hematologic biomarkers among patients undergoing maintenance hemodialysis. Compared with patients using an arteriovenous fistula (AVF), those using a hemodialysis catheter exhibited significantly higher neutrophil-to-lymphocyte ratio (NLR) and hemoglobin levels. Although ferritin levels did not differ significantly between the two groups in the unadjusted analysis, vascular access type remained independently associated with ferritin levels after adjustment for potential confounding factors. These findings suggest that vascular access type may influence inflammatory and hematologic profiles in maintenance hemodialysis patients and further support the clinical preference for AVF as the vascular access of choice whenever feasible. Future prospective multicenter studies with longitudinal follow-up and comprehensive assessment of inflammatory and anemia-related biomarkers are warranted to clarify the mechanisms underlying these associations and their impact on long-term clinical outcomes.

### Limitations of the Study

However, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference. Second, the study was conducted at a single tertiary referral center, which may limit the generalizability of the findings. Third, residual confounding cannot be excluded because detailed information regarding inflammatory markers such as C-reactive protein or interleukin-6, dialysis adequacy, erythropoiesis-stimulating agent dosage, intravenous iron therapy, and transfusion history was unavailable. Finally, the relatively modest sample size may have limited the statistical power to detect smaller differences between vascular access groups.

## Declarations

### Ethics approval and consent to participate

This study was approved by the institutional Health Research Ethics Committee.

### Competing interests

The authors declare no conflicts of interest.

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### Author's Contribution

Idea/concept: GFR. Design: GFR. Control/supervision: RTKD, DP, DR, EPP. Data collection/ processing: GFR. Analysis/interpretation: GFR. Literature review: -. Writing the article: GFR. Critical review: RTKD, DP, DR, EPP. 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

# Risk Factors Associated with Intradialytic Hypotension among Patients with Stage 5 Chronic Kidney Disease on Hemodialysis at a Tertiary Referral Hospital in Banjarmasin Indonesia: A Retrospective Cross-sectional Study

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**ABSTRACT**

***Background:*** Intradialytic hypotension (IDH) remains one of the most frequent acute complications of maintenance hemodialysis. Local data from Indonesian hemodialysis units remain limited, although patient characteristics, dialysis practices, comorbidity burden, and nutritional status may influence IDH risk.

***Objective:*** This study aimed to identify patient-related and dialysis-related factors associated with IDH among CKD-5HD patients at Ulin General Hospital, Banjarmasin, Indonesia.

***Methods:*** This retrospective cross-sectional study used secondary medical record data from adult patients with stage 5 chronic kidney disease undergoing maintenance hemodialysis at Ulin General Hospital, Banjarmasin, Indonesia. Patient-related and dialysis-related factors were evaluated. Variables with $p<0.25$ in bivariate analysis entered a multivariable binary logistic regression model.

***Results:*** A total of 145 patients were included. IDH occurred in 72 patients (49.66%). In multivariable analysis, age >=60 years was associated with higher odds of IDH compared with age <60 years (adjusted prevalence odds ratio [aPOR] 3.537, 95% confidence interval [CI] 1.185-10.562, p=0.024). Compared with body mass index (BMI) >=30 kg/m2, BMI 23.0-24.9 kg/m2 was associated with lower odds of IDH (aPOR 0.101, 95% CI 0.015-0.677, p=0.018).

***Conclusion:*** Nearly half of CKD-5HD patients experienced IDH. Older age, BMI category, antihypertensive medication burden, and pre-hemodialysis blood pressure category were associated with IDH. These findings support structured IDH risk assessment in routine hemodialysis care, especially among older patients and patients with severe pre-hemodialysis hypertension.

***Keywords:*** chronic kidney disease; hemodialysis; intradialytic hypotension; body mass index; antihypertensive agents; blood pressure.

## Introduction

Chronic kidney disease (CKD) is a major global health problem and contributes substantially to morbidity, health-care utilization, and mortality. The increasing number of patients with advanced CKD has expanded the need for kidney replacement therapy, including maintenance hemodialysis. In Indonesia, registry data show a growing burden of patients receiving dialysis, which makes dialysis safety a relevant clinical and public health issue.[1,2]

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Intradialytic hypotension (IDH) is among the most common acute complications during hemodialysis. Its reported frequency varies because studies use different definitions, blood pressure thresholds, symptom requirements, and session-based or patient-based measurements.[3–5] IDH may impair dialysis tolerance, reduce delivered dialysis dose, precipitate myocardial and cerebral hypoperfusion, increase vascular access complications, and contribute to adverse cardiovascular outcomes and mortality.[5–8]

The pathophysiology of IDH is multifactorial. Ultrafiltration reduces intravascular volume. A stable blood pressure response depends on adequate plasma refilling, vascular tone, baroreflex function, cardiac reserve, and neurohormonal compensation. Older age, diabetes, cardiovascular disease, nutritional status, excessive ultrafiltration, interdialytic weight gain, dialysate factors, and antihypertensive therapy have all been linked to IDH, although findings vary across populations.[7–13]

Evidence from Indonesian hemodialysis populations remains limited. Local patient profiles may differ from those in large international cohorts because of differences in comorbidity pattern, nutritional status, dialysis frequency, access type, and blood pressure management. This study aimed to identify patient-related and dialysis-related factors associated with IDH among CKD-5HD patients at Ulin General Hospital, Banjarmasin, Indonesia.

## Methods

### Study design and setting

This retrospective cross-sectional study used secondary medical record data from patients with stage 5 CKD undergoing maintenance hemodialysis (CKD-5HD). The study was conducted at the Hemodialysis Unit of Ulin General Hospital, Banjarmasin, Indonesia. Data extraction and analysis were performed after ethical and institutional approvals were obtained.

### Study population

The target population consisted of all CKD-5HD patients. Total sampling was used. All patients who fulfilled the eligibility criteria during the observation period from January to December 2025 were included. Inclusion criteria were age >=18 years, CKD-5HD for at least 3 months, hemodialysis one to three times per week with 4-5 hours per session, and complete medical records for hemodialysis blood pressure monitoring, ultrafiltration volume, intradialytic events, comorbidities, and relevant laboratory data. Exclusion criteria were acute or non-regular hemodialysis, dialysis at more than one facility during the observation period, hypotension from non-intradialytic causes such as acute bleeding, septic shock, or severe arrhythmia, incomplete key medical record data, intermittent dialysis after kidney transplantation, and inpatient status for any indication during the study period.

### Outcome definition

The dependent variable was IDH. IDH was defined as a decrease in systolic blood pressure of at least 20 mmHg or a decrease in mean arterial pressure of at least 10 mmHg from pre-dialysis measurement to the intradialytic nadir, accompanied by symptoms such as dizziness, weakness, nausea, or cramps, or requiring clinical intervention such as saline administration or interruption of ultrafiltration.

### Variables

Independent variables included patient-related factors and dialysis-related factors. Patient-related factors were age, sex, body mass index (BMI), dialysis vintage, hypertension category based on pre-hemodialysis blood pressure, diabetes mellitus, heart disease, antihypertensive medication use, hemoglobin concentration, and albumin concentration. Dialysis-related factors were interdialytic weight gain (IDWG), ultrafiltration volume, ultrafiltration rate (UFR), and vascular access type.

Age was categorized as <60 years and >=60 years. BMI was categorized using Asian cutoffs: <18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, and >=30.0 kg/m2. Pre-hemodialysis blood

pressure was categorized as non-hypertensive (<140/90 mmHg), grade I hypertension (140-159/90-99 mmHg), grade II hypertension (160-179/100-109 mmHg), and grade III hypertension (>=180/>=110 mmHg). IDWG was categorized as <3%, 3-5%, and >5%. Antihypertensive medication use was categorized as no medication, 1-2 agents, 3-4 agents, and >4 agents.

### Statistical analysis

Data were analyzed using IBM SPSS Statistics version 26. Categorical variables are presented as frequencies and percentages. Numerical variables are presented as mean +/- standard deviation or median with minimum and maximum values, according to distribution. Bivariate associations were tested using the chi-square test for categorical variables. The independent t test was used for normally distributed numerical variables, and the Mann-Whitney U test or nonparametric testing was used for non-normal numerical variables. A two-sided p value <0.05 was considered statistically significant.

Variables with p<0.25 in bivariate analysis were entered into a multivariable binary logistic regression model using the enter method. Results are reported as adjusted prevalence odds ratios (aPORs) with 95% confidence intervals (CIs). Because the outcome was common, odds ratios were interpreted as measures of association rather than direct estimates of relative risk.

## Results

### Baseline characteristics

A total of 145 CKD-5HD patients met the eligibility criteria. IDH occurred in 72 patients (49.66%), while 73 patients (50.34%) did not experience IDH. The mean age was 50.21 +/- 11.41 years. Most patients were aged <60 years (77.24%) and male (53.10%). Heart disease and hypertension were common, affecting 88.97% and 93.10% of the cohort, respectively. Grade III pre-hemodialysis hypertension was the most frequent blood pressure category (31.72%). The median dialysis vintage was 12 months (range 3-168), and the mean UFR was 7.81 +/- 3.73 mL/kg/hour. Detailed baseline characteristics are shown in Table 1.

### Bivariate analysis

In bivariate analysis, heart disease (p=0.032), pre-hemodialysis blood pressure category (p=0.009), and hemoglobin level (p=0.031) were significantly associated with IDH. Age >=60 years showed a clinically relevant but statistically borderline association with IDH (POR 2.093, 95% CI 0.940-4.662, p=0.068). BMI category (p=0.088), diabetes mellitus (p=0.186), dialysis vintage (p=0.208), and antihypertensive medication category (p=0.244) met the pre-specified p<0.25 threshold for multivariable modeling. Sex, UF, UFR, albumin level, IDWG, and vascular access type did not meet this threshold. Bivariate findings are summarized in Table 2.

### Multivariable analysis

In the multivariable logistic regression model, age >=60 years was independently associated with increased odds of IDH compared with age <60 years (aPOR 3.537, 95% CI 1.185-10.562, p=0.024). BMI 23.0-24.9 kg/m2 was associated with lower odds of IDH compared with BMI >=30.0 kg/m2 (aPOR 0.101, 95% CI 0.015-0.677, p=0.018). BMI 18.5-22.9 kg/m2 showed a protective trend that did not reach statistical significance (aPOR 0.188, 95% CI 0.034-1.028, p=0.054).

Compared with no antihypertensive medication use, the use of 1-2 agents (aPOR 0.049, 95% CI 0.003-0.849, p=0.038), 3-4 agents (aPOR 0.025, 95% CI 0.002-0.420, p=0.010), and >4 agents (aPOR 0.006, 95% CI 0.000-0.134, p=0.001) was associated with lower odds of IDH. Compared with grade III hypertension, grade II hypertension (aPOR 0.309, 95% CI 0.103-0.923, p=0.036), grade I hypertension (aPOR 0.166, 95% CI 0.052-0.530, p=0.002), and non-hypertensive pre-hemodialysis blood pressure (aPOR 0.029, 95% CI 0.006-0.132, p<0.001) were associated with lower odds of IDH. The final model is shown in Table 3.

## Discussion

This study found a high patient-level occurrence of IDH among CKD-5HD patients at a tertiary referral hospital in Indonesia. IDH affected 49.66% of included patients. The main independent factors associated with IDH were older age, BMI category, antihypertensive medication category, and pre-hemodialysis blood pressure category. These findings strengthen the need for individualized IDH risk assessment rather than reliance on a single dialysis-related variable.

Older age showed the most consistent risk-increasing association. Patients aged >=60 years had more than threefold higher odds of IDH after adjustment for other variables. This finding agrees with the biological model of IDH in which adequate blood pressure during ultrafiltration depends on plasma refilling, baroreflex sensitivity, arterial compliance, peripheral vasoconstriction, and cardiac reserve. Aging reduces baroreflex responsiveness and increases arterial stiffness, which limits compensatory vasoconstriction during intravascular volume reduction.[4,5,14] Older patients may also have a higher burden of diastolic dysfunction, ischemic heart disease, autonomic dysfunction, and frailty, all of which can reduce hemodynamic reserve during dialysis.

BMI showed a non-linear association with IDH. A BMI of 23.0-24.9 kg/m2 was associated with substantially lower odds of IDH compared with BMI >=30.0 kg/m2. In hemodialysis patients, BMI does not reliably distinguish muscle mass, adiposity, edema, and fluid overload. Patients with high BMI may have higher adipose tissue burden, endothelial dysfunction, inflammation, arterial stiffness, and absolute ultrafiltration requirements. Conversely, patients with very low BMI may have protein-energy wasting or sarcopenia. Recent studies suggest that body composition, rather than BMI alone, may better predict IDH risk.[15–17] The present finding supports the use of BMI as an initial screening measure, but it also highlights the need for body composition assessment, nutritional evaluation, and dry-weight reassessment in future studies.

Pre-hemodialysis blood pressure category was strongly associated with IDH. Patients with grade III hypertension before dialysis had the highest odds of IDH, while lower blood pressure categories showed lower odds. This finding may appear counterintuitive because hypotension is often expected in patients with low baseline pressure. However, severe pre-dialysis hypertension can indicate chronic volume overload, arterial stiffness, sympathetic activation, or cardiovascular disease. These conditions may require more aggressive fluid removal and may reduce the ability to tolerate rapid intravascular volume changes. Previous work has shown that predialysis blood pressure and IDH have complex, non-linear relationships, and that both very low and very high predialysis pressure profiles may reflect unstable hemodynamics.[7,8]

The inverse association between the number of antihypertensive agents and IDH requires cautious interpretation. This finding should not be interpreted as evidence that increasing antihypertensive medication prevents IDH. Medication number is a proxy for multiple clinical factors, including treatment indication, blood pressure severity, residual kidney function, cardiovascular disease, timing of administration, drug dialyzability, and physician selection. The predominant use of calcium channel blockers and angiotensin receptor blockers in the cohort may have influenced this association. Prior studies suggest that IDH risk differs more clearly by drug class, timing, and pharmacokinetic profile than by medication count alone.[10,18–20] Future research should evaluate antihypertensive class, dose, timing before dialysis, interdialytic blood pressure, and adherence.

Several variables that are commonly associated with IDH in the literature did not remain independently associated in this study. Diabetes mellitus, heart disease, dialysis vintage, hemoglobin, IDWG, UF, UFR, albumin, and vascular access type were not independent predictors in the final model. These results do not

exclude their biological relevance. Diabetes may affect IDH through autonomic neuropathy and cardiovascular disease. Heart disease risk may depend on ejection fraction, diastolic function, valvular disease, arrhythmia burden, and ischemia rather than a broad binary diagnosis. UFR and UF may require session-level analyses because patient-level summary measures can obscure intradialytic hemodynamic patterns. Albumin analysis was limited by incomplete data.[21–25]

This study has practical implications. Hemodialysis units should consider structured IDH risk screening using age, pre-hemodialysis blood pressure, nutritional or anthropometric profile, and medication review. Older patients and patients with grade III pre-dialysis hypertension may need closer blood pressure monitoring, careful reassessment of dry weight, review of ultrafiltration goals, consideration of longer or more frequent dialysis when fluid removal targets are high, and individualized antihypertensive timing. Routine clinical protocols should identify early symptoms of hypoperfusion, such as nausea, weakness, yawning, cramps, dizziness, and altered consciousness, before severe blood pressure decline occurs. This study adds local evidence from an Indonesian tertiary referral hemodialysis unit and evaluates multiple patient-related and dialysis-related variables in one model. The use of total sampling reduced selection bias within the defined clinical setting.

## Conclusion

IDH occurred in 49.66% of CKD-5HD patients at Ulin General Hospital, Banjarmasin. Age >=60 years increased the odds of IDH, while BMI 23.0-24.9 kg/m2 was associated with lower odds compared with BMI >=30.0 kg/m2. Antihypertensive medication category and pre-hemodialysis blood pressure category were also associated with IDH. These findings support individualized IDH prevention strategies that combine age-based risk assessment, nutritional and body composition evaluation, medication review, and careful pre-dialysis blood pressure management.

## Limitations of the Study

However, several limitations should be noted. First, the retrospective cross-sectional design limits causal inference. Second, the sample size was modest for a multivariable model with several predictors, which may produce wide confidence intervals and unstable estimates. Third, the study used medical record data, so measurement and documentation quality may vary. Fourth, heart disease was analyzed as a broad categorical variable without detailed echocardiographic or biomarker data. Fifth, antihypertensive analysis used medication count rather than drug class, dose, timing, dialyzability, or adherence. Sixth, albumin data were incomplete. Finally, the study did not use session-level repeated measures, which may better capture dynamic changes in ultrafiltration, blood pressure, and symptoms during dialysis.

## Declarations

### Ethics approval and consent to participate

The study protocol received ethical approval from the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Universitas Lambung Mangkurat (No. 047/KEPK-FKIK ULM/EC/VI/2026), and research permission from the Director of Ulin General Hospital (No. 63/PPDS IPD/Litbang/RSUDU/V/2026). The study used anonymized secondary medical record data, and all identifiable patient information was removed from the analytic dataset.

### Competing interests

The authors declare no competing interests.

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**Author's Contribution**

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**Original Article**

# Persistent Hypertension Awareness Gap and Temporal Trends in Indonesia: A 16-Year Analysis of National Health Surveys

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**ABSTRACT**

***Background:*** Hypertension is a key modifiable risk factor for cardiovascular and chronic kidney diseases. In Indonesia, surveys show a high prevalence based on measurements, but healthcare detection remains limited.
***Objective:*** To analyze trends in measured hypertension, physician-diagnosed hypertension and the diagnostic gap in Indonesia over a 16-year period.
***Methods:*** This secondary analysis used nationally representative surveys (Riskesdas 2007, 2013, 2018, and SKI 2023). Adults ≥18 years were included. Measured hypertension was defined as systolic ≥140 mmHg and/or diastolic ≥90 mmHg. Diagnosed hypertension was based on self-reported physician diagnosis or antihypertensive use. The diagnostic gap was the difference between measured and diagnosed prevalence.
***Results:*** Measured hypertension remained high (25.8%–34.1%), while diagnosed cases were low (7.2%–9.4%). The diagnostic gap persisted: 24.5 percentage points (2007), decreased to 16.4 (2013), then increased to 25.7 (2018) and remained high at 22.2 (2023). Overall, only a minority of individuals were aware of their condition. This gap was consistent across sociodemographic groups and regions.
***Conclusion:*** The hypertension diagnostic gap in Indonesia remains substantial and has tended to widen. Detection efforts have not kept pace with disease burden, highlighting the need to strengthen early screening and diagnosis to reduce cardiovascular and kidney disease risk.
***Keywords:*** hypertension; diagnostic gap; underdiagnosis; Indonesia; national health survey; chronic kidney disease.

## Introduction

Chronic Hypertension is one of the leading modifiable risk factors for cardiovascular disease, stroke, chronic kidney disease, and premature death worldwide. The World Health Organization (WHO) identifies hypertension as a major cause of global morbidity and mortality and estimates that only a minority of adults with hypertension have their blood pressure adequately controlled. WHO has also emphasized that improving detection, treatment, and control of hypertension at the primary care level is essential to reducing avoidable cardiovascular events and deaths (World Health Organization.[1]

The burden of hypertension is especially challenging in low- and middle-income countries, where health systems often face limitations in screening coverage, continuity of care, treatment adherence, and risk-factor control. Because hypertension is frequently asymptomatic, many individuals remain unaware of their condition until complications occur. This makes case detection through routine blood pressure measurement a critical component of prevention strategies.[1]

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In Indonesia, the burden of hypertension has been documented repeatedly through nationally representative health surveys. Across survey waves, prevalence based on blood pressure measurement has consistently been substantially higher than prevalence based on physician diagnosis. In 2007, national hypertension prevalence was 31.7% by measurement and 7.2% by diagnosis.[2] By 2013, these estimates were 25.8% and 9.4%, respectively.[3] In 2018, measured prevalence rose to 34.11% while diagnosed prevalence was 8.36%.[4] In 2023, measured prevalence remained high at 30.8%, whereas diagnosed prevalence was only 8.6%.[5]

This discrepancy between measured and diagnosed hypertension represents a diagnostic gap, reflecting the difference between the underlying burden of disease and the proportion recognized by the healthcare system. Such a gap is clinically important because delayed diagnosis may postpone lifestyle intervention, pharmacologic treatment, and long-term risk reduction. From a kidney health perspective, this is especially relevant because blood pressure control is a key strategy for reducing cardiovascular risk and slowing progression of chronic kidney disease.[6]

Although Indonesian national survey reports provide yearly estimates of hypertension prevalence, the long-term pattern of the diagnostic gap itself has not been sufficiently framed as a health-system performance issue. Examining this gap over time may provide a more policy-relevant perspective than prevalence alone, because it helps identify whether increasing disease burden has been matched by improvements in detection.

Therefore, this study aimed to analyze the 16-year trend in measured hypertension, physician-diagnosed hypertension, and the resulting diagnostic gap in Indonesia using national health survey data from 2007 to 2023. In addition, this study explored variation in the diagnostic gap across provinces and sociodemographic groups to identify populations at greater risk of remaining undiagnosed.

## Methods

### Study Design

This study was a secondary analysis of nationally representative cross-sectional surveys conducted in Indonesia over a 16-year period, including the Basic Health Research (Riskesdas) surveys in 2007, 2013, and 2018, and the Indonesian Health Survey (Survei Kesehatan Indonesia, SKI) in 2023.

### Data Sources

All data were obtained from publicly available national survey reports published by the Ministry of Health of Indonesia. These surveys used multistage cluster sampling to represent the Indonesian population at national and provincial levels.

### Study Population

The analysis included individuals aged ≥18 years who had available data on blood pressure measurement and/or hypertension diagnosis. For consistency across survey years, only adult population estimates (≥18 years) were used for trend comparison.

### Definition of Variables

**Table 1.** Operational Definitions of Study Variables

| Variable | Operational Definition |
|---|---|
| Measured Hypertension | Defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg based on survey measurements, in accordance with JNC VII criteria. Blood pressure was measured at least twice using a digital sphygmomanometer, and the average of measurements was used for analysis. |
| Diagnosed Hypertension | Defined as self-reported history of hypertension diagnosed by a healthcare professional or current use of antihypertensive medication. |
| Diagnostic Gap | Defined as the absolute difference between measured hypertension prevalence and diagnosed hypertension prevalence at the population level. |
| Undiagnosed Hypertension | Defined as individuals with measured hypertension who had not been previously diagnosed by a healthcare professional. |

### Study Variables

Sociodemographic variables included age group, sex, education level, occupation, place of residence (urban versus rural), and socioeconomic status as measured by wealth quintiles. These variables were extracted and analyzed as reported in each national survey, ensuring consistency with the original data classification.

### Statistical Analysis

Descriptive analyses were performed to evaluate trends in hypertension prevalence across survey years. Measured hypertension prevalence, diagnosed hypertension prevalence, and the diagnostic gap were calculated for each survey period. The diagnostic gap was defined as the difference between measured and diagnosed hypertension and was expressed both as an absolute difference in percentage points and as a relative proportion of diagnosed cases among total hypertension cases.

Temporal trends were assessed descriptively across survey waves to identify patterns over time. Where data were available, subgroup analyses were conducted based on sociodemographic characteristics to explore variations in hypertension prevalence and diagnostic gaps among different population groups. All analyses were based on aggregated national estimates as reported in official survey publications.

## Results

### Trends in Hypertension Prevalence and Diagnosis

Across the four national survey waves, the prevalence of hypertension based on blood pressure measurement remained consistently high, whereas the prevalence based on physician diagnosis remained substantially lower.

In 2007, the prevalence of hypertension based on measurement was 31.7%, while only 7.2% of individuals reported a prior diagnosis. By 2013, measured prevalence was 25.8% and diagnosed prevalence increased slightly to 9.4%. In 2018, measured prevalence rose sharply to 34.11%, whereas diagnosed prevalence remained low at 8.36%. In 2023, measured prevalence remained elevated at 30.8%, with diagnosed prevalence at 8.6%.

### Diagnostic Gap Across Survey Years

The diagnostic gap between measured and diagnosed hypertension persisted throughout the study period and showed a tendency to widen over time.

In 2007, the gap was 24.5 percentage points. This decreased to 16.4 percentage points in 2013, followed by a marked increase to 25.7 percentage points in 2018. In 2023, the gap remained substantial at 22.2 percentage points.

When expressed as proportions, only approximately one-quarter to one-third of individuals with hypertension were aware of their condition across survey years.

**Table 2.** National Trends in Measured and Diagnosed Hypertension in Indonesia (2007–2023)

| Year | Measured Hypertension (%) | Diagnosed Hypertension (%) | Diagnostic Gap (%) |
|---|---|---|---|
| 2007 | 31.7 | 7.2 | 24.5 |
| 2013 | 25.8 | 9.4 | 16.4 |
| 2018 | 34.11 | 8.36 | 25.75 |
| 2023 | 30.8 | 8.6 | 22.2 |

### Variation by Sociodemographic Characteristics

Across all survey years, measured hypertension prevalence increased with age, with the highest prevalence observed in older age groups. Similarly, diagnosed hypertension was more common among older individuals; however, the relative diagnostic gap persisted across all age categories.

Women consistently had higher rates of diagnosed hypertension compared to men, although measured hypertension remained high in both groups.

Individuals with lower levels of education exhibited higher prevalence of measured hypertension, while diagnosis rates did not increase proportionally, indicating a larger diagnostic gap in lower socioeconomic groups.

Urban populations tended to have slightly higher diagnosed hypertension compared to rural populations, although measured prevalence remained comparable, suggesting disparities in access to detection services.

### Provincial Variation

Substantial variation in hypertension prevalence and diagnosis was observed across provinces. Provinces with higher measured prevalence did not consistently demonstrate higher diagnosis rates, further indicating uneven detection capacity across regions.

Overall, these findings highlight a persistent and substantial diagnostic gap in hypertension across Indonesia, with evidence of widening disparities over time and across population subgroups.

## Discussion

This study demonstrates a persistent and substantial diagnostic gap in hypertension in Indonesia over a 16-year period, with the gap exceeding 20 percentage points in recent years. Although the prevalence of hypertension based on blood pressure measurement remained high, the proportion of individuals diagnosed by healthcare providers has not improved proportionally. This indicates that increases in disease burden have not been accompanied by adequate improvements in population-level detection.

### Principal Findings

The most notable finding is the widening diagnostic gap, particularly between 2013 and 2018, when measured hypertension increased markedly while diagnosed cases remained relatively unchanged. Even in 2023, despite slight improvements, the gap remained large. These findings suggest that a substantial proportion of individuals with hypertension continue to be unaware of their condition, highlighting a persistent limitation in early detection strategies.

**Comparison with Global Evidence**

The findings of this study are consistent with global evidence indicating that underdiagnosis of hypertension remains a major challenge, particularly in low- and middle-income countries (LMICs). The World Health Organization (WHO) reports that globally, nearly half of individuals with hypertension are unaware of their condition.[1] Similarly, large-scale analyses from the NCD Risk Factor Collaboration have shown that although hypertension prevalence has increased over time, improvements in awareness and treatment have been uneven, particularly in LMIC settings.[7]

Compared to high-income countries, where systematic screening and primary care integration have improved hypertension detection rates, many LMICs continue to experience substantial gaps between disease prevalence and diagnosis. The persistence of a large diagnostic gap in Indonesia suggests that the country faces similar structural challenges in translating epidemiological burden into effective detection and management.

**Health System and Behavioral Explanations**

Several mechanisms may explain the persistent diagnostic gap observed in this study. First, hypertension is largely asymptomatic, which reduces perceived need for medical evaluation. Individuals may not seek care until complications occur, thereby limiting opportunities for early diagnosis.

Second, screening coverage may remain insufficient. Although Indonesia has implemented national programs targeting non-communicable diseases, routine blood pressure measurement may not yet be consistently integrated into all levels of primary healthcare or community-based services. Opportunistic screening, which has been effective in other settings, may still be underutilized.

Third, disparities in healthcare access and utilization likely contribute to unequal detection. The larger diagnostic gap observed among individuals with lower socioeconomic status and education levels suggests the influence of structural barriers, including limited access to healthcare facilities, lower health literacy, and reduced health-seeking behavior. Previous studies have highlighted that social determinants of health play a critical role in shaping access to diagnosis and treatment for chronic conditions.[7]

Fourth, health system factors such as workforce capacity, continuity of care, and follow-up mechanisms may also limit effective diagnosis. Fragmentation in care delivery and insufficient integration between preventive and curative services may reduce the likelihood that individuals with elevated blood pressure are formally diagnosed and managed.

**Clinical and Nephrology Implications**

From a clinical perspective, the high proportion of undiagnosed hypertension has important implications. Prolonged exposure to elevated blood pressure without treatment increases the risk of cardiovascular events, stroke, and target organ damage. Early diagnosis is essential to initiate lifestyle modification and pharmacological therapy to reduce these risks.

In the context of nephrology, undiagnosed hypertension represents a critical risk factor for the development and progression of chronic kidney disease (CKD). Hypertension is both a cause and a consequence of kidney disease, and uncontrolled blood pressure accelerates the decline in renal function. Clinical guidelines emphasize that early detection and effective blood pressure control are key strategies for slowing CKD progression and reducing the need for renal replacement therapy.[6] Therefore, failure to detect hypertension at an early stage may contribute to the increasing burden of advanced kidney disease in Indonesia.

**Public Health and Policy Implications**

The findings of this study have important implications for public health policy. Strengthening hypertension detection requires a multi-level approach. First, expanding routine blood pressure screening in primary care, workplaces, and community settings is essential. Integrating opportunistic screening into all

patient encounters may help identify undiagnosed cases.

Second, improving public awareness of hypertension as a "silent disease" is critical. Educational campaigns targeting high-risk populations may encourage earlier health-seeking behavior and increase participation in screening programs.

Third, addressing disparities in access to healthcare is necessary to reduce inequities in detection. Targeted interventions for populations with lower socioeconomic status, including community outreach and mobile health services, may help bridge this gap.

Fourth, strengthening primary healthcare systems is essential to ensure continuity of care, follow-up, and appropriate management after diagnosis. Integration of hypertension screening into broader non-communicable disease control programs may improve efficiency and impact.

This study has several strengths, including the use of nationally representative data across multiple time points, allowing for a comprehensive assessment of long-term trends. The use of standardized definitions across surveys enhances comparability.

## Conclusion

The diagnostic gap in hypertension in Indonesia remains substantial and reflects ongoing challenges in early detection. Despite a high and increasing burden of hypertension, detection strategies have not improved proportionally. Addressing this gap through strengthened screening, improved access to care, and increased public awareness is essential to reduce the burden of cardiovascular and kidney disease.

## Limitations of the Study

However, several limitations should be acknowledged. First, the analysis was based on aggregated data, limiting the ability to perform individual-level statistical analysis. Second, variations in survey methodology across years may affect comparability. Third, self-reported diagnosis may be subject to recall bias, potentially underestimating or overestimating true diagnosis rates.

## Declarations

### Ethics approval and consent to participate

This study used publicly available secondary data from national surveys. No individual-level identifiable information was accessed; therefore, ethical approval was not required.

### Competing interests

There are no conflicts of interest in writing this article.

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### Author's Contribution

Idea/concept: SAI. Design: SAI. Control/supervision: DN. Data collection/ processing: SAI, DN. Analysis/interpretation: SAI, DN. Literature review: SAI. Writing the article: SAI. Critical review: -. 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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Case Report

# Diagnostic Challenge of Cardiorenal Involvement in Active Systemic Lupus Erythematosus: Lupus Nephritis with Rapidly Progressive Renal Dysfunction: A Case Report

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**ABSTRACT**

Renal and cardiac involvement in active systemic lupus erythematosus (SLE) may pose a diagnostic challenge because clinical, serological, and histopathological findings do not always correlate. A 20-year-old woman with a history of SLE presented with edema, foamy urine, decreased urine output, arthralgia, oral ulcers, and orthopnea. Laboratory and imaging findings revealed severe proteinuria, hematuria, urinary casts, hypocomplementemia, elevated serum creatinine, heart failure with reduced ejection fraction with an ejection fraction of 37%, pericardial effusion, and cardiomegaly. Kidney biopsy demonstrated class III+V lupus nephritis, with an activity index of 8/24, chronicity index of 8/12, fibrous and fibrocellular crescents each found in 1 of 5 viable glomeruli, and 60% interstitial fibrosis/tubular atrophy. Immunofluorescence showed granular deposition of IgG, IgA, IgM, C3, and C1q. Although the clinical course resembled rapidly progressive glomerulonephritis, the non-dominant crescentic lesions made "rapid decline in kidney function" a more appropriate term than classic RPGN. Cardiac dysfunction may represent suspected myocardial involvement, volume overload, anemia, uremia, or a combination of these factors. Kidney biopsy and integrated cardiac evaluation are essential for assessing disease activity, chronicity, and prognosis in cardiorenal involvement of active SLE.

**Keywords:** systemic lupus erythematosus; lupus nephritis; cardiorenal involvement; rapid decline in kidney function; kidney biopsy

## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse clinical manifestations. The disease may involve the skin, joints, kidneys, heart, lungs, nervous system, and hematologic system. Major organ involvement is clinically important because it is associated with irreversible organ damage, long-term immunosuppressive therapy, and increased morbidity and mortality.[1]

The kidney is one of the most clinically significant organs affected in SLE. Lupus nephritis may present with isolated proteinuria, hematuria, urinary casts, nephrotic syndrome, nephritic syndrome, acute kidney dysfunction, or rapid deterioration of kidney function. This broad spectrum often complicates clinical assessment because laboratory findings do not always correlate with histopathological severity. Proteinuria, hematuria, serum creatinine, complement levels, and anti-dsDNA antibodies

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may suggest renal activity. Still, they cannot reliably determine the histological class, degree of active inflammation, or the extent of chronic damage.[2]

Kidney biopsy has the important role in the diagnosis and management of lupus nephritis. It establishes the histopathological class, identifies active and chronic lesions, detects additional pathological findings, and helps estimate response to treatment. The 2024 kidney disease: Improving Global Outcomes (KDIGO) guideline emphasizes that biopsy reports should describe both activity and chronicity because these parameters influence therapeutic decisions and prognosis.[2] Active lesions, such as endocapillary hypercellularity, wire-loop lesions, cellular or fibrocellular crescents, and interstitial inflammation, indicate potentially reversible inflammation. In contrast, chronic lesions, including glomerulosclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis, generally represent irreversible damage.[2,3]

A diagnostic challenge arises when a patient with SLE develops rapid deterioration of kidney function, but the biopsy findings do not fully support classic rapidly progressive glomerulonephritis (RPGN). Clinically, RPGN is characterized by hematuria, proteinuria, oliguria, and rapidly progressive renal failure. In lupus nephritis, this presentation is usually associated with severe proliferative glomerulonephritis and extensive crescentic lesions.[4,5] However, not all patients with rapid renal decline have dominant crescents. In such cases, the term "rapid decline in kidney function" may be more accurate than classic RPGN or crescentic lupus nephritis.

Cardiac involvement may further complicate the clinical picture in patient. SLE may affect the pericardium, myocardium, valves, conduction system, coronary arteries, and pulmonary vasculature.[6] Heart failure in active SLE may reflect lupus myocarditis, but it may also result from volume overload, anemia, uremia, hypertension, infection, or ischemic heart disease. Differentiating these mechanisms is important because treatment decisions and prognosis differ. Echocardiography, cardiac biomarkers, electrocardiography, and cardiac magnetic resonance imaging may help clarify the underlying cause of myocardial dysfunction.[7]

This case report describes a young woman with active SLE who developed class III+V lupus nephritis, rapid decline in kidney function, heart failure with reduced ejection fraction, and pericardial effusion. The case illustrates how renal and cardiac manifestations may overlap in active SLE and highlights the importance of integrating clinical, serological, histopathological, and cardiac findings before assigning a final diagnosis and prognosis.

## Case Presentation

A 20-year-old woman presented to the emergency department with progressive swelling of both lower extremities, followed by facial edema. She also reported abdominal distension, foamy urine, reduced urine output of approximately 400–600 mL/day, intermittent arthralgia, fluctuating fever, and dyspnea in the supine position requiring two pillows.

The patient had been diagnosed with SLE in 2023 at the age of 17 years, initially presenting with arthralgia and skin rash. She had received hydroxychloroquine and methylprednisolone with dose adjustments but had no previous diagnosis of kidney involvement. Before referral, she was treated at another hospital for impaired kidney function and received intravenous methylprednisolone 500 mg daily for three days, followed by oral methylprednisolone. A kidney biopsy had not been performed at that time.

On admission, she appeared moderately ill and was fully conscious. Blood pressure was 114/76 mmHg, pulse rate 92 beats/minute, respiratory rate 19 breaths/minute, temperature 36.7°C, and oxygen saturation 97% on room air. Physical examination revealed pale conjunctiva, shifting dullness, and bilateral pitting edema. There was no active joint swelling or tenderness. Disease activity was considered high, with a minimum SLEDAI-2K score of 14 based on hematuria, proteinuria, pyuria, and pericardial effusion. Because pyuria and positive nitrite may

also indicate urinary tract infection, renal activity was interpreted together with proteinuria, hematuria, urinary casts, hypocomplementemia, previous high anti-dsDNA level, and biopsy findings.

Laboratory evaluation showed anemia, elevated blood urea nitrogen, impaired kidney function, active urinary sediment, and nephrotic-range proteinuria. The urine protein-to-creatinine ratio was 6302 mg/g on Day 1 and 4969 mg/g on evaluation Day 4. Urinalysis showed albumin 4+, blood 2+, positive nitrite, leukocyte esterase 2+, leukocytes 226/high-power field, erythrocytes 108/high-power field, positive casts, and bacteria. Complement levels were low, with C3 of 67 mg/d and C4 of 10 mg/dL. Previous immunological data showed ANA positivity >1:1000 and anti-dsDNA of 2430.

Serial renal function tests showed severe but fluctuating kidney impairment, with serum creatinine ranging from 2.83 to 5.03 mg/dL during evaluation. These findings, together with reduced urine output, active urinary sediment, severe proteinuria, and hypocomplementemia, supported rapid decline in kidney function in the setting of active SLE.

Chest radiography showed cardiomegaly and left pleural effusion. Follow-up imaging demonstrated persistent cardiomegaly with blunting of the left costophrenic angle, suggesting minimal pleural effusion or pleural thickening. Kidney ultrasonography showed chronic parenchymal kidney disease. Echocardiography revealed reduced left ventricular systolic function, with an ejection fraction of 37%, and pericardial effusion. Electrocardiography showed sinus rhythm with T-wave inversion in leads V5, V6, I, aVL, II, and III. The initial cardiac assessment was heart failure with reduced ejection fraction, with suspected myocardial involvement in the context of active SLE.

Kidney biopsy showed glomerulonephritis with focal endocapillary proliferation in 2 of 5 glomeruli. Fibrous and fibrocellular crescents were each found in 1 of 5 viable glomeruli. Severe chronic tubulointerstitial injury was also present, with interstitial fibrosis/tubular atrophy reaching 60%. Immunofluorescence examination showed a granular pattern with IgG, IgA, IgM, C3, and C1q deposition, supporting immune-complex glomerulonephritis consistent with lupus nephritis. Based on the clinical, serological, and histopathological findings, the diagnosis was considered compatible with class III+V lupus nephritis.

During hospitalization, the patient received supportive therapy and baseline SLE treatment, including hydroxychloroquine, methylprednisolone, intravenous diuretics, antihypertensive therapy, renin-angiotensin system blockade, beta-blocker, spironolactone, bicarbonate, calcium carbonate, vitamin D, and ceftriaxone for urinary tract infection. Cyclophosphamide was planned after infection control and hemoglobin optimization.

## Discussion

This case illustrates the complexity of interpreting renal and cardiac manifestations in active SLE. The patient presented with edema, foamy urine, oliguria, nephrotic-range proteinuria, hematuria, urinary casts, hypocomplementemia, and elevated serum creatinine. These findings strongly suggested active lupus nephritis. However, the biopsy showed not only active inflammatory lesions, but also substantial chronic kidney damage. At the same time, the patient had heart failure with reduced ejection fraction, pericardial effusion, cardiomegaly, orthopnea, and electrocardiographic abnormalities. Therefore, the main diagnostic challenge was not merely establishing the presence of lupus nephritis but determining how much of the renal dysfunction was still potentially reversible and whether the cardiac dysfunction was caused by primary lupus cardiac involvement, secondary cardiorenal mechanisms, or both.

The diagnosis of lupus nephritis was supported by the patient's clinical history of SLE, urinary findings, serological profile, and kidney biopsy. Severe proteinuria and edema reflected a nephrotic component, while hematuria, urinary casts, oliguria, and impaired kidney function suggested nephritic activity. This mixed phenotype was explained by the biopsy result of class III+V lupus nephritis. Class III lupus nephritis represents focal proliferative disease and may account for hematuria, urinary casts, and kidney dysfunction. Class V lupus nephritis represents membranous involvement and is commonly associated with heavy proteinuria and edema. Thus, the patient's clinical presentation was not contradictory, but rather consistent with combined proliferative and membranous lupus nephritis.[2,4]

Although the patient developed rapid deterioration of kidney function, the term classic RPGN should be used cautiously. In this case, the clinical picture resembled RPGN because the patient had hematuria, proteinuria, oliguria, and rapidly worsening renal function. However, the biopsy did not show dominant crescentic glomerulonephritis. Crescents were found in only 2 of 5 viable glomeruli, consisting of one fibrous crescent and one fibrocellular crescent, without cellular crescents. Chen et al. reported that RPGN in lupus nephritis is usually associated with a high crescent burden, with a mean crescent percentage of 57.0 ± 23.2%, and that crescent proportion was an important prognostic factor for end-stage kidney disease.[5] The present patient had limited crescentic involvement compared with this description. Therefore, in this patient, "rapid decline in kidney function" is a more precise clinical term than classic RPGN or crescentic lupus nephritis.

This distinction is clinically important because rapid renal decline in lupus nephritis may result from several mechanisms, not only crescent formation. In this patient, renal dysfunction likely reflected a combination of active proliferative lesions, immune-complex deposition, tubulointerstitial inflammation, severe proteinuria, infection-related stress, and pre-existing chronic kidney damage. The kidney ultrasound also suggested chronic parenchymal kidney disease, which was later supported by biopsy findings. Therefore, the deterioration of kidney function should be interpreted as the result of both active lupus nephritis and chronic structural injury, rather than as purely acute crescentic disease.

The biopsy was the key examination because it clarified the balance between active and chronic lesions. The activity index was 8/24, indicating ongoing inflammation that may still respond to immunosuppressive therapy. Active lesions included endocapillary proliferation, immune-complex deposition, fibrocellular crescent, and interstitial inflammation. These findings supported the plan for induction therapy. However, the chronicity index was also high at 8/12, and interstitial fibrosis/tubular atrophy reached 60%. These findings suggest that a substantial component of kidney injury was already irreversible. KDIGO 2024 emphasizes that active and chronic lesions should be reported because they provide information beyond histological class and help guide treatment and prognosis.[2] In this patient, the activity index justified immunosuppression, whereas the chronicity index and extensive IF/TA indicated that complete renal recovery might be limited.

Immunofluorescence findings further strengthened the diagnosis. The granular deposition of IgG, IgA, IgM, C3, and C1q was consistent with immune-complex glomerulonephritis typical of lupus nephritis. Parikh et al. described the full-house immunofluorescence pattern as a classic feature of lupus nephritis, although it is not mandatory for diagnosis.[4] In the present case, this pattern supported the interpretation that the renal findings were related to SLE rather than another isolated glomerular disease. However, the limited number of glomeruli in the biopsy specimen should be considered when interpreting lesion distribution and crescent burden.

The management plan in this case should be understood, considering both disease activity and treatment risk. Active class III or IV lupus nephritis, with or without a class V component,

generally requires glucocorticoids combined with immunosuppressive therapy. KDIGO 2024 recommends glucocorticoids with mycophenolic acid analogs, low-dose intravenous cyclophosphamide, belimumab-based regimens, or selected calcineurin inhibitor-based regimens, depending on clinical context and kidney function.[2] EULAR and ACR recommendations also support the use of glucocorticoids with mycophenolate or cyclophosphamide as the backbone of therapy for active lupus nephritis.[8,9] In this patient, cyclophosphamide was considered reasonable because of proliferative lupus nephritis, severe proteinuria, and significant renal dysfunction. Nevertheless, treatment was appropriately delayed until infection and anemia were addressed, because immunosuppression in the presence of active infection and poor hematologic status may increase complications.

The cardiac findings created another layer of diagnostic uncertainty. The patient had HFrEF with an ejection fraction of 37%, pericardial effusion, orthopnea, cardiomegaly, and T-wave inversion. In active SLE, pericardial effusion may represent serositis, whereas reduced ejection fraction raises the possibility of lupus myocarditis. However, lupus myocarditis cannot be diagnosed based on reduced ejection fraction alone. In this patient, several alternative or contributing mechanisms were present, including volume overload from renal dysfunction, anemia, uremia, hypoalbuminemia, and systemic inflammation. These factors may independently worsen cardiac function or mimic primary myocardial involvement.

The available data were sufficient to suspect cardiac involvement, but not enough to confirm lupus myocarditis. Serial cardiac biomarkers, NT-proBNP, repeat echocardiography after volume optimization, global longitudinal strain, and cardiac magnetic resonance imaging would have helped distinguish inflammatory myocardial disease from secondary hemodynamic dysfunction. Luo et al. emphasized the role of cardiac magnetic resonance imaging in evaluating myocardial edema, inflammation, fibrosis, systolic function, and subclinical myocardial involvement in SLE.[10] In this patient, the absence of advanced cardiac evaluation limited diagnostic certainty. Therefore, the cardiac diagnosis should be stated carefully as HFrEF with suspected lupus myocardial involvement and possible secondary cardiorenal contribution.

The renal and cardiac abnormalities in this patient should not be interpreted separately. From the kidney-to-heart perspective, severe lupus nephritis may cause sodium and water retention, hypoalbuminemia, anemia, uremia, renin-angiotensin-aldosterone system activation, and increased hemodynamic burden. These mechanisms can worsen congestion and reduce cardiac performance. From the heart-to-kidney perspective, reduced left ventricular systolic function may impair renal perfusion, increase venous congestion, and reduce diuretic responsiveness, thereby worsening kidney function. This bidirectional interaction supports the concept of cardiorenal involvement in active SLE rather than two unrelated organ problems.

The case also has therapeutic implications. Fluid management should balance the need to relieve congestion against the risk of worsening renal perfusion. Renin-angiotensin system blockade may help reduce proteinuria and support heart failure management, but it requires careful monitoring in severe renal dysfunction. Diuretics are necessary for volume control, yet response may be limited by reduced kidney function and hypoalbuminemia. Immunosuppression may control lupus activity, but high chronicity on biopsy means that improvement in serum creatinine may be incomplete. These considerations should be communicated clearly to the patient and family so that treatment goals are realistic: controlling inflammatory activity, reducing proteinuria, stabilizing kidney function, managing heart failure symptoms, preventing infection, and slowing progression to chronic kidney disease.

Comparison with previous reports supports the relevance of simultaneous renal and cardiac involvement in active SLE. Karanović Štambuk et al. reported severe SLE with lupus myocarditis and proliferative lupus nephritis,

presenting with acute heart failure, reduced ejection fraction, nephrotic-range proteinuria, active urinary sediment, hypocomplementemia, and elevated cardiac biomarkers.[11] The present case shares several features, including active lupus nephritis, reduced ejection fraction, and serological activity. However, unlike that report, the diagnosis of lupus myocarditis in this patient could not be confirmed because cardiac magnetic resonance imaging, serial biomarkers, and endomyocardial biopsy were not available. This difference reinforces the importance of cautious wording and comprehensive cardiac evaluation.

Several limitations should be acknowledged. First, the biopsy specimen contained only 5 glomeruli, while the immunofluorescence assessment included only 2 glomeruli. This may limit the representation of the true extent of proliferative and crescentic lesions. Second, electron microscopy was not available, although it could have provided additional information regarding electron-dense deposits and basement membrane changes. Third, cardiac assessment was incomplete because serial troponin, NT-proBNP, cardiac magnetic resonance imaging, and endomyocardial biopsy were not performed. Fourth, long-term outcomes, including proteinuria response, creatinine trajectory, need for dialysis, and recovery of ejection fraction, were not yet available.

Overall, this case demonstrates that active SLE with cardiorenal manifestations requires careful integration of clinical and pathological data. The renal presentation suggested severe active disease, but the biopsy showed that chronic damage was already substantial. The cardiac findings raised suspicion of lupus-related myocardial involvement, but secondary mechanisms related to renal dysfunction and systemic illness remained plausible. Therefore, this case supports the importance of kidney biopsy, cautious terminology, structured cardiac evaluation, and multidisciplinary management in patients with active SLE and overlapping renal and cardiac dysfunction.

## Conclusion

This case demonstrates the diagnostic challenge of cardiorenal involvement in active SLE, presenting with biopsy-confirmed class III+V lupus nephritis, rapid decline in kidney function, HFrEF, and pericardial effusion. Although the renal presentation resembled RPGN clinically, the limited crescentic lesions made "rapid decline in kidney function" a more accurate term than classic RPGN or crescentic lupus nephritis. Kidney biopsy was essential for identifying both active inflammatory lesions and severe chronic damage, which influenced treatment decisions and prognosis. Cardiac dysfunction should also be interpreted cautiously because it may reflect suspected lupus myocardial involvement, secondary effects of kidney dysfunction, anemia, uremia, or a combination of these mechanisms. An integrated multidisciplinary approach is required to guide treatment and provide a realistic prognosis.

## Declarations

### Ethics approval and consent to participate

This case report was prepared in accordance with the CARE guidelines. Written informed consent for publication was obtained from the patient.

### Competing interests

The authors declare no conflicts of interest related to this manuscript.

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### Author's Contribution

Idea/concept: SYAP. Design: SYAP. Control/supervision: NA, KH. Data collection/ processing: SYAP. Analysis/interpretation: SYAP. Literature review: -. Writing the article: SYAP. Critical review: NA, KH. 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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