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Association Between Indoxyl Sulfate Levels and Major Cardiovascular Events in Hemodialysis Patients with Chronic Kidney Disease

Adi Suhendra [1*], Sumi Ramadani [2], Radar Radius Tarigan [2]

[1] *Internal Medicine Study Program, Faculty of Medicine, University of North Sumatra*
[2] *Department of Internal Medicine, Faculty of Medicine, University of North Sumatra*

***Corresponding Author**: Adi Suhendra, Email: adisuhendra75@gmail.com

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ABSTRACT

Introduction: Chronic kidney disease (CKD) markedly reduces quality of life and increases mortality risk, predominantly due to cardiovascular complications. Indoxyl sulfate, a protein-bound uremic toxin, is increasingly recognized for its role in accelerating cardiovascular disease in CKD patients. This study aims to evaluate the association between indoxyl sulfate levels and major cardiovascular events (MCE) in patients with stage 5 CKD undergoing hemodialysis.

Methods: This observational case-control study included 50 patients with stage 5 CKD on hemodialysis. Inclusion criteria were informed consent, willingness to undergo laboratory assessments, and a confirmed CKD diagnosis. Patients with a history of acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, cardiac arrest, arrhythmias, or incomplete laboratory data were excluded. Serum indoxyl sulfate, creatinine, urea, and estimated glomerular filtration rate (eGFR) were measured. Statistical analyses, including t-tests and logistic regression, were used to compare clinical parameters between patients with and without MCE.

Results: Of the 50 patients (mean age: 55.4 ± 8.2 years for MCE group, 47.8 ± 7.9 years for non-MCE group; p=0.015), 29 experienced MCE, and 21 did not. Hemodialysis duration averaged 15.9 ± 4.3 years (MCE) versus 25.9 ± 5.1 years (non-MCE; p=0.005). Significant differences were found in creatinine (p=0.014), creatinine-urea ratio (p=0.007), and eGFR (p<0.001). Elevated indoxyl sulfate levels were strongly associated with MCE (p=0.001).

Conclusion: Higher indoxyl sulfate levels are significantly correlated with major cardiovascular events in hemodialysis-dependent CKD patients, underscoring its potential as a predictive biomarker for cardiovascular risk.

Keywords

Chronic Kidney Disease, Hemodialysis, Indoxyl Sulfate, Major Cardiovascular Events, Uremic Toxin

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INTRODUCTION

Chronic kidney disease (CKD) represents a significant global public health challenge because of its high incidence, hospitalization rates, substantial economic burden, and poor prognosis, all of which profoundly affect the quality of life of patients. CKD markedly increases the risks of end-stage renal disease (ESRD), cardiovascular disease (CVD), and mortality. Advanced stages of CKD are characterized by elevated complication and mortality rates. Globally, an estimated 697.5 million individuals (9.1% of the population) are affected by CKD [1]. Between 1990 and 2017, CKD-related deaths increased by 41.5%, making it the 12th leading cause of death worldwide in 2017, with projections indicating that it could become the fifth leading cause by 2040 [1]. Epidemiological data on CKD in Indonesia remain limited. The 2018 Basic Health Research

(Riskesdas) reported an increase in CKD prevalence from 0.2% in 2013 to 0.3% in 2018 [2,3]. Despite limited prevalence data, the number of patients requiring renal replacement therapy, particularly hemodialysis, has surged [3]. Chronic hemodialysis is costly, with kidney failure ranking as the fourth highest healthcare expenditure in Indonesia in 2021, following heart disease, cancer, and stroke [4]. CKD development is associated with various risk factors, and Indonesia is currently undergoing an epidemiological transition in which non-communicable diseases are becoming increasingly prominent [5-7].

Progressive renal function loss in CKD is closely linked to immune dysregulation, particularly uremia, which induces a paradoxical state of immune activation and suppression in CKD patients. In patients with ESRD, uremia-related immune activation, such as hypercytokinemia and inflammation, increases the cardiovascular risk. Concurrently, impaired immune responses increase susceptibility to infections, reduce vaccine efficacy, and increase risk. Cardiovascular disease and infections are the leading causes of death in patients with ESRD, and both are intricately associated with uremia-induced immune dysfunction. Retention of uremic toxins and cytokines in ESRD patients fosters oxidative stress and a proinflammatory milieu, altering the immune system composition and function [8]. Among the 100 identified uremic toxins, indoxyl sulfate (IS) and p-cresyl sulfate (PCS), which are derived from the microbial fermentation of tryptophan and tyrosine in the gut, are strongly associated with adverse outcomes in renal failure. These amino acids are metabolized into indoles and p-cresol in the large intestine and subsequently converted to IS and PCS in the liver. Patients with ESRD exhibit significantly elevated serum IS levels compared with healthy individuals [8]. Research has primarily focused on IS-mediated endothelial dysfunction to explain its role in cardiovascular pathology [9].

Indoxyl sulfate, a key protein-bound uremic toxin originating from indole, a tryptophan metabolite in the gut microbiome, accumulates in renal insufficiency due to impaired clearance and exerts deleterious effects on multiple organs. Preclinical studies have linked IS to renal tubular cell damage, tubulointerstitial fibrosis, cardiac fibrosis, vascular calcification, and atherosclerosis. Clinical evidence increasingly suggests that IS contributes to cardiovascular disease and mortality in patients [10]. High-density lipoprotein (HDL) cholesterol is traditionally protective against cardiovascular disease in the general population via reverse cholesterol transport, which removes excess cholesterol from lipid-laden macrophages and the peripheral tissues. HDL also exerts anti-inflammatory, antioxidant, and antithrombotic effects, potentially mediated by components such as apolipoprotein E, apolipoprotein A-IV, and apolipoprotein J; however, the precise mechanisms remain unclear [11].

Patients with cardiovascular disease face a secondary risk of major cardiovascular events (MCEs), including all-cause mortality, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization [12]. The definition of MCEs varies across studies since 1990, with common components including heart failure, non-fatal reinfarction, angina recurrence, rehospitalization, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and mortality [13]. In Indonesia, a 2018 study at Sanglah General Hospital, Denpasar, evaluated hypertension as a predictor of MCEs in patients with acute myocardial infarction and assessed outcomes such as cardiovascular death, cardiogenic shock, heart failure, and lethal arrhythmias [14]. The 2018 Qanita study on coronary heart disease reported rehospitalization due to myocardial infarction as the most frequent MCE, with incidences of 2.9% at 30 days and 4.8% at 6 months [15]. The prevalence of all-cause mortality within one year in patients with heart failure and coronary artery disease ranges from 13.7% to 38% based on studies from Australia, Canada, the Czech Republic, Denmark, France, Italy, Japan, and the United States [14]. Assessing MCEs and their risk factors is critical for optimizing therapeutic strategies and health outcomes. Traditional MCE risk factors include sex, age, total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, systolic blood pressure, smoking, and diabetes, which reflect the severity of coronary artery disease progression and its potential to cause heart failure [16].

Dyslipidemia is prevalent in CKD and is characterized by low HDL cholesterol (HDL-C) levels, elevated triglycerides, and oxidized LDL cholesterol [11]. In CKD, HDL composition and function are altered, diminishing its protective effects and potentially transforming it into a toxic entity [11]. These findings suggest that both low and high serum HDL-C levels may adversely affect kidney function in non-dialysis patients with

CKD [11]. Thus, this study aimed to elucidate the complex interplay between serum HDL-C levels and CKD progression risk in CKD patients.

This study aimed to investigate the prevalence of chronic kidney disease (CKD) and the association between indoxyl sulfate levels and major cardiovascular events (MCEs) in patients with CKD undergoing hemodialysis. The specific objectives were (1) to characterize CKD patients, (2) to measure indoxyl sulfate levels in CKD patients on hemodialysis, and (3) to evaluate the relationship between indoxyl sulfate levels and MCEs in CKD patients on hemodialysis.

METHODS

Study Design and Population This cross-sectional study was conducted at Haji Adam Malik General Hospital, Medan, Indonesia, targeting patients diagnosed with chronic kidney disease (CKD) at the time of study approval by the Health Research Ethics Committee of the University of North Sumatra/Haji Adam Malik General Hospital. The study population comprised patients with CKD who received treatment at the hospital during the study period. Participants were selected using consecutive sampling, and all eligible patients who met the predefined inclusion and exclusion criteria were enrolled. The inclusion criteria included a confirmed CKD diagnosis based on clinical and laboratory assessments, age ≥18 years, and ongoing hemodialysis treatment. Exclusion criteria encompassed Patients with incomplete medical records, acute kidney injury, or those unwilling to participate in the study were excluded. The sample size was determined to ensure adequate statistical power based on the expected prevalence of major cardiovascular events (MCEs) in patients with CKD.

Demographic and clinical data were retrieved from medical records, including age, sex, and comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease. Laboratory measurements of indoxyl sulfate levels were performed using standardized biochemical assays. Blood samples were collected under fasting conditions, processed, and analyzed in the hospital's certified laboratory to ensure accuracy. Major cardiovascular events (MCEs), defined as all-cause mortality, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization due to cardiovascular causes, were identified and verified through a medical record review. All data collection procedures adhered to standardized protocols to minimize bias and ensure data integrity.

Table 1. Summary of Study Variables and Analytical

Variable	Description	Measurement Method	Statistical Analysis
Demographic Data	Age, gender, comorbidities (e.g., hypertension, diabetes, cardiovascular disease)	Retrieved from medical records	Descriptive statistics (mean ± SD, frequency, %)
Indoxyl Sulfate Levels	Serum concentration of indoxyl sulfate	Biochemical assay (fasting blood samples)	Independent t-test or Mann-Whitney U test
Major Cardiovascular Events (MCEs)	All-cause mortality, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization	Medical record review	Chi-Square test or Fisher Exact test
Data Normality	Assessment of distribution for continuous variables	Kolmogorov-Smirnov test	Determines use of parametric/non-parametric tests

Notes: This table outlines the key variables, their measurement methods, and corresponding statistical analyses employed in the study, ensuring a systematic and transparent approach to data handling and interpretation.

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki and approved by the Health Research Ethics Committee of the University of North Sumatra/Haji Adam Malik General Hospital. Written informed consent was obtained from all participants before data collection. Patient confidentiality was maintained by anonymizing the data and restricting access to authorized personnel. The

study commenced with ethical approval, ensuring that all procedures complied with the institutional and national ethical guidelines.

Descriptive statistics were used to summarize demographic and clinical characteristics, with continuous variables presented as means ± standard deviations or medians (interquartile ranges) depending on the data distribution, and categorical variables were expressed as frequencies and percentages. The normality of continuous variables, such as indoxyl sulfate levels, was assessed using the Kolmogorov-Smirnov test. Differences in indoxyl sulfate levels between the groups with and without MCEs were analyzed using the independent t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Associations between categorical variables, such as the presence of MCEs and demographic or clinical factors, were evaluated using the chi-square test, with the Fisher Exact test applied when expected cell counts were low. All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

RESULTS

Demographic and Clinical Characteristics The study enrolled 56 patients with grade 5 chronic kidney disease (CKD) undergoing hemodialysis at Haji Adam Malik General Hospital, Medan, Indonesia. Patients were categorized based on the presence or absence of major cardiovascular events (MCEs). Table 1 shows the demographic and laboratory characteristics of the study population. Of the total cohort, 31 patients (55.4%) experienced MCEs, whereas 25 patients (44.6%) did not. The MCE group had a higher proportion of female patients than the non-MCE group (26.8% vs. 16.1 %), although this difference was not statistically significant (p=0.421). The mean age was significantly higher in the MCE group (55.5 ± 9.1 years) compared to the non-MCE group (46.0 ± 12.1 years; p=0.002).

Table 1. Demographic and Laboratory Characteristics of Study Participants

Characteristics	MCE (n=31)	Non-MCE (n=25)	Total (n=56)	p-value
Sex, n (%)				0.421
Male	16 (28.6)	16 (28.6)	32 (57.1)	
Female	15 (26.8)	9 (16.1)	24 (42.9)	
Age (years), Mean ± SD	55.5 ± 9.1	46.0 ± 12.1	51.2 ± 11.5	0.002*
CKD Grading, n (%)				-
Grade 5	31 (55.4)	25 (44.6)	56 (100)	
Duration of HD (years), Mean ± SD	16.5 ± 14.2	27.8 ± 13.3	21.6 ± 14.9	0.001*
Hemoglobin Level (g/dL), Mean ± SD	8.4 ± 1.3	8.7 ± 1.5	8.5 ± 1.4	0.410
Urea Level (mg/dL), Mean ± SD	128.2 ± 46.6	127.6 ± 54.7	127.9 ± 49.9	0.965
Creatinine Level (mg/dL), Mean ± SD	10.5 ± 3.9	8.3 ± 4.1	9.6 ± 4.1	0.043*
Urea/Creatinine Ratio, Mean ± SD	12.9 ± 4.6	17.0 ± 6.7	14.7 ± 6.0	0.010*
eGFR (mL/min/1.73 m^2), Mean ± SD	5.3 ± 2.7	9.2 ± 3.6	7.0 ± 3.7	<0.001*
Indoxyl Sulfate Level (x10^3 µg/L), Mean ± SD	2.0 ± 0.5	1.6 ± 0.2	1.8 ± 0.4	<0.001*

Notes: MCE, major cardiovascular event; CKD, chronic kidney disease; HD, hemodialysis; eGFR, estimated glomerular filtration rate; SD, standard deviation.

All participants had CKD grade 5, reflecting the focus of the study on advanced renal disease. The mean duration of hemodialysis was significantly shorter in the MCE group (16.5 ± 14.2 years) compared to the non-MCE group (27.8 ± 13.3 years; p=0.001). Laboratory parameters revealed no significant differences in hemoglobin (p=0.410) or urea levels (p=0.965) between the groups. However, significant differences were observed in creatinine levels (p=0.043), urea-to-creatinine ratio (p=0.010), estimated glomerular filtration rate (eGFR; p<0.001), and indoxyl sulfate levels (p<0.001), with the MCE group exhibiting higher creatinine levels, lower urea-to-creatinine ratios, lower eGFR, and elevated indoxyl sulfate levels compared to the non-MCE group.

The distribution of Major Cardiovascular Events Among the 31 patients with MCEs is summarized in Table 2. Congestive heart failure (CHF) was the most common MCE, affecting 15 patients (48.3%), followed

by myocardial infarction in 7 patients (22.8%). Arrhythmia was observed in four patients (12.9%), while death and cardiogenic shock occurred in three (9.6%) and two (6.4%) patients, respectively. These findings highlight CHF as the predominant cardiovascular complication in this CKD cohort, underscoring its clinical significance in patients undergoing hemodialysis.

Table 2. Distribution of Major Cardiovascular Events (MCEs)

MCE Classification	Number, n (%) (n=31)
Death	3 (9.6)
Congestive Heart Failure (CHF)	15 (48.3)
Cardiogenic Shock	2 (6.4)
Arrhythmia	4 (12.9)
Myocardial Infarction	7 (22.8)

Notes: The distribution of major cardiovascular events (MCEs) among 31 patients with CKD on hemodialysis, with congestive heart failure (CHF) being the most frequent (48.3%), followed by myocardial infarction (22.8%), arrhythmia (12.9%), death (9.6%), and cardiogenic shock (6.4%).

Association between indoxyl sulfate levels and major cardiovascular diseases The relationship between indoxyl sulfate levels and MCEs was analyzed (Table 3). Patients with MCEs had significantly higher mean indoxyl sulfate levels (2.0 ± 0.5 x10^3 µg/L) than those without MCEs (1.6 ± 0.2 x10^3 µg/L; p=0.001). This finding suggests a strong association between elevated indoxyl sulfate levels and the occurrence of MCEs in patients with CKD on hemodialysis, supporting the hypothesis that indoxyl sulfate may contribute to cardiovascular risk in this population.

Table 3. Association of Indoxyl Sulfate Levels with Major Cardiovascular Events (MCEs)

Variable	MCE (n=31)	Non-MCE (n=25)	p-value
Indoxyl Sulfate Level (x10^3 µg/L), Mean ± SD	2.0 ± 0.5	1.6 ± 0.2	0.001*

Notes: MCE, major cardiovascular event; SD, standard deviation.

Summary of Findings: The results indicate significant differences in age, hemodialysis duration, creatinine levels, urea-to-creatinine ratio, eGFR, and indoxyl sulfate levels between CKD patients with and without MCEs. The predominance of CHF among MCEs underscores its burden in this population. The statistically significant association between elevated indoxyl sulfate levels and MCEs highlights the potential role of this uremic toxin as a biomarker or contributor to cardiovascular risk in CKD patients undergoing hemodialysis. These findings provide a foundation for further investigation of the mechanistic pathways linking indoxyl sulfate to cardiovascular outcomes.

DISCUSSION

This study revealed that the majority of the 56 CKD patients on hemodialysis were male (57.1%), consistent with previous research by Fan et al. (2019), who reported a 67% male prevalence (p=0.851) [13], Iwasaki et al. (2024) with 57% [14], and Barreto et al. (2009) with 60% [15]. However, no significant sex-based difference was observed between the MCE and non-MCE groups (P =0.421), suggesting that sex may not be a primary determinant of MCE risk in this population. Age differences were significant, with the MCE group being older (55.5 ± 9.1 years) than the non-MCE group (46.0 ± 12.1 years; p=0.002), aligning with Fan et al. (2019), who reported mean ages of 74 and 68 years for MCE and non-MCE groups, respectively (p=0.019) [13]. Takkavatakarn et al. (2021) and Iwasaki et al. (2024) reported mean ages of 63.5 and 75 years, respectively, further supporting the association between advanced age and cardiovascular risk in CKD [14,16]. The shorter hemodialysis duration in the MCE group (16.5 ± 14.2 years) compared to the non-MCE group (27.8 ± 13.3 years; p=0.001) contrasts with studies by Li et al. (2022) and Cao et al. (2015), which reported mean hemodialysis durations of 49 and 43.2 months, respectively [17,18]. This discrepancy may reflect the differences in disease progression and treatment access.

Laboratory parameters showed no significant differences in hemoglobin (p=0.410) or urea levels (p=0.965) between groups, consistent with Cao et al. (2015), who reported a mean blood urea nitrogen (BUN) of 142.4 mg/dL [18], but differed from Fan et al. (2019), who found significant hemoglobin differences (p=0.032) [13]. Lin et al. (2012) reported a lower mean BUN of 44.2 mg/dL, possibly due to variations in dialysis adequacy or patient characteristics [19]. Creatinine levels were significantly higher in the MCE group (10.5 ± 3.9 mg/dL) compared to the non-MCE group (8.3 ± 4.1 mg/dL; p=0.043), corroborating Fan et al. (2019) (p<0.001) [13], though Takkavatakarn et al. (2021) and Lin et al. (2012) reported lower mean creatinine levels (4.06 and 3.76 mg/dL, respectively) [16,19]. The eGFR was significantly lower in the MCE group (5.3 ± 2.7 mL/min/1.73 m²) compared to the non-MCE group (9.2 ± 3.6 mL/min/1.73 m²; p<0.001), consistent with Fan et al. (2019) [13], but contrasting with higher eGFR values reported by Takkavatakarn et al. (2021) (22.49 mL/min/1.73 m²) and Barreto et al. (2009) (37 mL/min/1.73 m²) [15,16]. These differences may reflect the varying stages of CKD or methodological differences in the eGFR estimation.

The definition of MCEs remains heterogeneous, with the FDA and EMA restricting MCEs to myocardial infarction, stroke, and cardiovascular mortality, whereas broader definitions include heart failure and hospitalization for cardiovascular procedures [20]. This study's MCE distribution, with congestive heart failure (48.3%) being the most common event, aligns with Bosco et al. (2021), who noted heart failure in 25.8% of studies as part of the MCE definitions [20]. The high prevalence of heart failure in this cohort may reflect CKD-related cardiac remodeling driven by indoxyl sulfate-induced collagen production and oxidative stress, leading to left ventricular hypertrophy and fibrosis [16,21]. These processes impair endothelial progenitor cell function and increase vascular calcification, further elevating MCE risk [13,16]. Interventions targeting indoxyl sulfate, such as AST-120, may mitigate fibrosis and oxidative stress, potentially reducing the incidence of [21]. The interplay between indoxyl sulfate, glomerular sclerosis, and an altered redox status underscores its role in CKD progression and cardiovascular complications [13,16,21].

Indoxyl sulfate levels were significantly higher in the MCE group (2.0 ± 0.5 x10³ µg/L) compared to the non-MCE group (1.6 ± 0.2 x10³ µg/L; p<0.001), consistent with Fan et al. (2019) (p<0.001) [13]. A significant association between indoxyl sulfate levels and MCEs was observed (p=0.001), supporting Fan et al. (2019) who linked higher indoxyl sulfate levels to increased MCE risk [13]. However, Takkavatakarn et al. (2021), Li et al. (2022), and (2012) found no significant association (p=0.069; p<0.01) [16-19], possibly due to differences in study populations, sample sizes, or indoxyl sulfate measurement techniques. Indoxyl sulfate, a uremic toxin derived from tryptophan metabolism, is implicated in vascular thrombosis, cardiac fibrosis, and oxidative stress, contributing to cardiovascular morbidity and mortality in CKD [21-24]. Its accumulation in renal insufficiency exacerbates inflammation, atherosclerosis, and vascular stiffness, consistent with the findings that high indoxyl sulfate levels correlate with heart failure and arrhythmias [25-27].

CONCLUSION

CKD patients on hemodialysis with MCEs were predominantly male, older (55.5 vs. 46.0 years), and had shorter hemodialysis duration (16.5 vs. 27.8 years) than those without MCEs. Significant differences in creatinine, urea-to-creatinine ratio, eGFR, and indoxyl sulfate levels were found, with higher indoxyl sulfate levels being strongly linked to MCEs (p=0.001), indicating its role as a critical cardiovascular risk biomarker in CKD.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to be published in the Journal of Society Medicine.

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The authors declare no conflicts of interest in this case report.

AUTHORS' CONTRIBUTIONS
All authors contributed to the work, including data analysis, drafting, and reviewing the article. They approved the final version and were accountable for all aspects.

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