International Journal of Research and Review
Vol. 10; Issue: 12; December 2023
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

The Relationship Between Indoxyl Sulfate Levels and Functional Ability of End-Stage Renal Disease Patients Undergoing Regular Haemodialysis Using the Karnofsky Scale Measuring Instrument at Haji Adam Malik Central General Hospital Medan

M. Ikhsan Fadillah[1], Syafrizal Nasution[2], Sumi Ramadani[2]

[1]Specialist Program in Internal Medicine, [2]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, University of North Sumatera, Medan, Indonesia.

Corresponding Author: M. Ikhsan Fadillah

DOI: https://doi.org/10.52403/ijrr.20231273

ABSTRACT

Background: ESRD is a burdensome disease with high prevalence, mortality, and treatment costs. Indoxyl sulfate is one of the most studied solutes accumulating in plasma when the kidneys fail. Clinical studies have shown that indoxyl sulfate can predict the prognosis of CKD and CVD in CKD patients. Serum levels of IS are associated with all-cause mortality and cardiovascular mortality in CKD patients. The general objective of this study was to determine the relationship between indoxyl sulfate levels and the functional ability of CKD patients undergoing regular hemodialysis using the Karnofsky scale measuring instrument at the Haji Adam Malik Central General Hospital Medan.
Methods: This research is an observational analytic study with a cross-sectional design. Data collection involved recording indoxyl sulfate levels in kidney failure patients undergoing hemodialysis at Haji Adam Malik Hospital.
Results: Of all 56 study samples, the mean age was 49.35 years, with a standard deviation of 12.3 years. Most patients were male, from the Batak ethnicity, with hypertension as the etiology. The mean indoxyl sulfate level was 47.32 µg/mL with a 29.19 µg/mL standard deviation. Most patients presented with functional ability calculated by Karnofsky score in category A. The analysis results with the Spearman test showed a moderate negative correlation between indoxyl sulfate levels and the functional ability of patients.
Conclusion: Indoxyl sulfate levels can be an objective parameter to predict a patient's functional ability.

Keywords: Indoxyl Sulfate, Haemodialysis, End Stage Renal Disease, Functional Ability

INTRODUCTION

End-stage renal disease (ESRD) has a prevalence of between 8% and 16% of the population worldwide. ESRD is defined by a glomerular filtration rate of less than 60 mL/min/1.73 m², albuminuria of at least 30 mg per 24 hours, or markers of kidney damage (e.g., hematuria or structural abnormalities such as polycystic or dysplastic kidneys) that persist for more than three months. ESRD is more common in developing countries than in developed countries. Globally, ESRD is most commonly due to diabetes or hypertension, but other causes such as glomerulonephritis, infections, and environmental exposures (such as air pollution, herbal remedies, and pesticides) can be expected in Asian countries, sub-Saharan Africa, and many developing countries.[1,2]

Renal replacement therapy, including dialysis and kidney transplantation, is required for patients who progress to end-stage renal disease (ESRD) (GFR <15 mL/min/1.73 m²). Patients with advanced ESRD have a 3.6-fold increased risk of death compared to the general population, with the risk further increasing to 9- to 12-fold for patients receiving dialysis treatment. The life expectancy of a 55-year-old patient with stage 5 ESRD is only about 5.6 years, and the life expectancy of ESRD patients is worse than some forms of cancer.[3,4]

ESRD is a burdensome disease with high prevalence, mortality, and medical costs. Glomerular filtration rate (GFR) is the most widely applied index of renal function in ESRD in clinical practice, but GFR measurement methods are cumbersome, expensive, and time-consuming in clinical settings. Thus, GFR is estimated by equations based on serum creatinine levels, such as GFR estimation, Modification of Diet in Renal Disease, and CKD Epidemiology Collaboration. However, creatinine formation is affected by age, gender, race, and body weight independently of GFR. As comorbidities are prevalent in patients with ESRD, a single biomarker is insufficient to evaluate disease progression. New biomarkers to predict ESRD progression are essential. Indoxyl sulfate, a protein-bound uremic toxin with its special biological characteristics and pathophysiological effects, might be a valuable new diagnostic surrogate to assess comorbidities in ESRD.[5]

Uremia is a complication of ESRD, defined as the accumulation of solutes usually cleared by the kidneys. If left untreated, uremia is a life-threatening condition. Although dialysis can prolong the survival of end-stage renal disease patients, it cannot completely alleviate the uremic condition, leaving patients with the so-called "residual syndrome." Despite regular dialysis treatment, incomplete removal of organic waste compounds results in the accumulation of uremic toxins, which play an essential role in the development of ESRD and cardiovascular disease (CVD).[3,4]

Uremic toxins are of three types: water-soluble small-sized molecules, medium-sized molecules, and protein-bound uremic toxins (PBUTs). Recent advances in dialysis treatments have improved the removal of water-soluble small and medium molecular weight uremic toxins; however, the removal of PBUTs by standard hemodialysis (HD) sessions is insufficient due to their high protein-bound nature. For example, indoxyl sulfate (IS), a representative of PBUT, is formed from indole produced in the gut. The protein-bound fraction in the blood is 98%, and the clearance with one conventional HD session is only 32%.[6-8]

Indoxyl sulfate is one of the most studied solutes accumulating in plasma when the kidneys fail. Originally called "indican," it was first isolated by Obermayer and Popper in 1911 and was noted to be in high concentrations in the blood of patients with kidney disease. Clinical interest initially focused on its role in non-renal disease as a "putrefaction" product of colon microbial metabolism. Studies in the 1950s testing the urinary excretion of indoxyl sulfate were associated with various conditions, particularly gastrointestinal and mental illness. As indoxyl sulfate was known to be cleared primarily by the kidneys and assays were available, interest shifted toward its potential role in kidney disease. Numerous studies have since assessed the contribution of indoxyl sulfate to the adverse effects of kidney disease.[9]

Indoxyl sulfate accumulation occurs early during the progression of Chronic Kidney Disease and contributes to renal dysfunction by inducing fibrosis, inflammation, oxidative stress, and tissue remodeling. The renal toxicity of high IS concentrations (250 μM) has been extensively explored, especially in tubular and glomerular cells.[31] Indoxyl sulfate is a small solute (MW = 213 g/mol) that, in >90%, is reversibly bound to

plasma proteins, especially to albumin; thus, tubular secretion is the main elimination pathway. However, at low dialytic clearance, dialysis patients show IS concentrations 10-20 times higher when compared to normal values.[10]

As a typical protein-bound uremic toxin, indoxyl sulfate was shown to play an essential role in ESRD by directly inducing renal damage, CVD, and bone disease through various mechanisms, as stated above. Clinical studies have shown that indoxyl sulfate can predict the prognosis of ESRD and CVD in ESRD patients. Serum levels of IS were associated with all-cause mortality and cardiovascular mortality in ESRD patients.[5]

Indoxyl sulfate is also able to predict the prevalence of ESRD-related complications such as aortic calcification, vascular stiffness, and heart failure. High indoxyl sulfate levels may indicate high renal, cardiovascular, bone damage, and mortality. Notably, indoxyl sulfate also plays a role in ESRD, CVD, and renal bone disease pathological processes. Interventions such as diet modification and administration of AST-120 significantly lowered serum IS levels. Indoxyl sulfate detection in ESRD patients may offer screening for a population at high risk of cardiovascular events. Continuous IS detection may help evaluate treatment effects and predict disease outcomes.[5]

To the best of the researcher's knowledge, although there have been many studies that have looked directly at the relationship between indoxyl sulfate and various hemodialysis parameters, there are no studies that can show the relationship between indoxyl sulfate levels and the functional capacity of patients. This assessment will help determine and screen possible rehabilitative measures that can be prescribed so that chronic kidney disease patients can have a good quality of life.

MATERIALS & METHODS

Study Design

This study employs an observational analytic approach with a cross-sectional design. The research involves collecting data to record indoxyl sulfate levels in patients experiencing renal failure and undergoing hemodialysis at Adam Malik Hospital.

Study Sample

The study population comprises patients diagnosed with chronic renal failure from May 2023 to July 2023, seeking treatment at Haji Adam Malik Medan Central General Hospital. The research sample was selected using a consecutive sampling method, considering specific criteria for inclusion and exclusion.

The inclusion criteria in this study were patients aged 18 or older, diagnosed with chronic renal failure, undergoing regular hemodialysis, willing to participate, and providing informed consent. Meanwhile, the exclusion criteria were incomplete laboratory examination results and hospitalized patients.

Data Extraction

The data collected for this study encompassed a diverse set of variables, including baseline characteristics of the study population (age, gender, ethnicity, duration of CKD, CKD grade, etiology, Karnofsky score) and laboratory characteristics (hemoglobin, leukocyte, thrombocyte, urea, creatinine, and indoxyl sulfate).

STATISTICAL ANALYSIS

Descriptive statistical analysis was applied to the demographic data. The normality test was conducted using the Kolmogorov-Smirnov test. Bivariate analysis was employed to assess chronic kidney disease at Haji Adam Malik Hospital, Medan. The research data underwent statistical analysis using the Windows SPSS (Statistical Product and Service Solutions) computer

program version 24.0, and statistical significance was determined at $p<0.05$.

RESULT

A total of 56 patients were enrolled in this study. The mean age of the participants was 49.35 years (±12.3), with a median age of 51.5 years, ranging from 25 to 75 years. Among the participants, 34 were male (60.7%), and 22 were female. Most belonged to the Batak ethnicity (62.5%), followed by Java ethnicity (21.4%).

The study population comprised patients diagnosed with chronic renal failure seeking treatment at Haji Adam Malik Central General Hospital in Medan from December 2022 to January 2023. The majority presented with grade 5 (82.1%), followed by grade 4 (17.9%). The average duration of chronic kidney failure was 2.8 years (±2.74), with a median duration of 2 years. Common comorbidities included hypertension (46.4%) and diabetes (24%). The Karnofsky scale assessed functional ability, with most patients falling into category A (62.5%). The baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline Characteristics of Study Population

Parameter	Mean (Range)	f	%
Age (Years)	51,5 (25–75)		
Gender			
Male		34	60,7
Female		22	39,3
Ethnicity			
Batak		35	62,5
Java		12	21,4
Aceh		5	8,9
Banjar		3	5,4
Minang		1	1,8
Duration of CKD (Years)	2 (0,41–11)		
Grade			
Grade 5		56	100
Etiology			
Diabetes		14	24
Hypertension		40	71,4
Uric Acid		9	16,1
History of Steroid Usage		1	1,8
Urolithiasis		2	3,6
Not Identified		6	10,7
Karnofsky Score			
50		6	10,7
60		7	12,5
70		8	14,3
80		18	32,1
90		17	30,4

Patients underwent laboratory examinations before hemodialysis, including urea, creatinine, leukocyte, and platelet levels. The mean values for hemoglobin, leukocytes, and platelets before hemodialysis were 9.2 ± 10.15, 7697 ± 2667, and 210,396 ± 83,628, respectively. Urea and creatinine levels were 161.89 mg/dL (±42.16) and 13.12 mg/dL (±3.8), respectively. Indoxyl sulfate levels, the independent variable in this study, were measured with an average of 47.32 µg/mL with a standard deviation of 29.19 µg/mL. The laboratory characteristics of the study population are presented on Table 2.

Table 2. Laboratory Characteristics of Study Population

Parameter	Mean (Range)
Hemoglobin	7,8 (5–83)
Leukocyte	7.410 (2.990–15.490)
Trombocyte	199.500 (34.200–482.000)
Urea (mg/dL)	153,5 (72–340)
Creatinine (mg/dL)	13,65 (4,3–20,4)
IS (µg/mL)	41,46 (6,31–10,99)

Demographic characteristics were analyzed using bivariate analysis. No significant association was found between gender and indoxyl sulfate levels (Mann-Whitney test, p-value = 0.524). Similarly, no association was observed between indoxyl sulfate levels and the duration of end-stage renal disease (Spearman test, p-value = 0.380, rho value = 0.120). These results are summarized in Table 3 and Figure 1.

Table 3. The Relationship Between Gender and Indoxyl Sulfate

Parameter	Indoxyl Sulfate	*p-value*
Gender		
Male	49,1 ± 29,91	0,524*
Female	44,55 ± 28,52	

*) Mann-Whitney Test

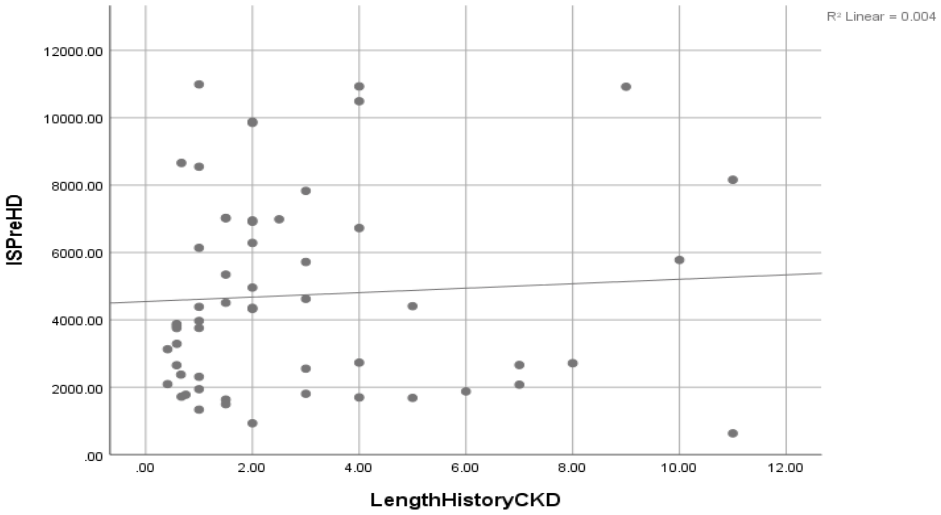

Figure 1. Scatter Diagram of the Duration of ESRD and Indoxyl Sulfate

The correlation between the independent variable (indoxyl sulfate levels) and the dependent variable (functional ability) was analyzed using the Spearman test. The analysis revealed a moderate negative correlation with an R-value of 0.588, as illustrated in Table 4 and Figure 2.

Table 4. The Relationship Between Indoxyl Sulfate and Functional Ability

Parameter	Indoxyl Sulfate	*p-value*
Karnofsky Score		
50	60,56 ± 26,7	
60	68,69 ± 26,4	< 0,001*
70	77,48 ± 29,77	
80	33,3 ± 18,58	
90	34,49 ± 23,96	

*) Kruskal-Wallis Test

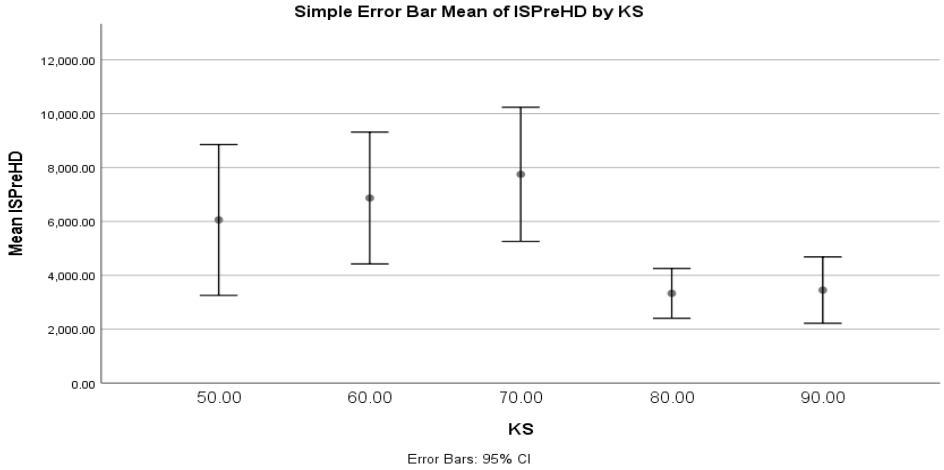

Figure 2. Boxplot Diagram of Indoxyl Sulfate Levels and Karnofsky Score

DISCUSSION

This study was conducted at Haji Adam Malik Central General Hospital in Medan with the approval of the University of North Sumatera's Faculty of Medicine Research Ethics Commission. Research and data collection took place from July 2023 to August 2023, involving 56 samples recruited based on statistical significance calculations.

Of the 56 samples, the mean age was 49.35 years, with a standard deviation of 12.3 years. This aligns with the research at Prof. Dr. R. D. Kandou Hospital in Manado by Poluan et al. in 2016, where chronic kidney disease predominantly occurred in the age group of 50-59 years, with 21 patients, followed by the age group of 60-69 years (20 patients), 40-49 years (16 patients), 70-79 years (8 patients), 30-39 years (3 patients), 20-29 years (2 patients), and 80-89 years (1 patient).[11]

Regarding gender, 34 patients were male, and 22 were female, consistent with the literature of Harris and Zhang in 2020, indicating a 50% higher incidence of End-Stage Renal Disease (ESRD) in adult men compared to women. However, it is crucial to note that the prevalence in women continues to increase due to hormonal protective factors before menopause, leading to a decrease in the incidence of hypertension and diabetic microvasculopathy, subsequently affecting the prevalence of ESRD and decelerating the decline in kidney function in ESRD patients without diabetes.[12]

Regarding ethnicity, 35 patients were Batak, constituting 62.5% of the total patients, followed by Javanese patients, 12 or 21.4%. This aligns with the data from Ariyosep Siregar in 2019, where the prevalence of ESRD patients in North Sumatra was 520 people, with 53.1% men and 46.9% women, and ethnic Batak accounting for 65.6% of cases.[13]

All patients seeking treatment at H. Adam Malik Medan Hospital presented with grade 5, totaling 56 people. This contrasts with the Suriyong et al. study (2022), which reported a prevalence of late-stage ESRD at 12% (7.7 - 17%) in Southeast Asia. The higher value in our study may be attributed to H. Adam Malik General Hospital's being a tertiary referral center where patients with complex and severe conditions are treated.[14]

Before hemodialysis, patients underwent laboratory tests, including urea, creatinine, leukocytes, and platelets. With standard deviations, the mean values of hemoglobin, leukocytes, and platelets before hemodialysis were 9.2 ± 10.15, 7697 ± 2667, and 210,396 ± 83,628, respectively. These results suggest a predilection for anemia in ESRD patients, consistent with the Bishaw et al. study in Ethiopia, where almost 85.34% of ESRD patients were anemic. Anemia in chronic kidney disease stems from various factors, with decreased renal production of erythropoietin (EPO) being the widely accepted etiology responsible for stimulating red blood cell production. Other contributing factors include uremia (causing RBC deformities leading to hemolysis), folate and vitamin B12 deficiency, iron deficiency, bleeding due to dysfunctional platelets, and, rarely, blood loss due to hemodialysis.[15]

Kidney function examinations, including urea and creatinine, were conducted before and after hemodialysis. The urea level before hemodialysis was 161.89 mg/dL with a standard deviation of 42.16, decreasing to 52.6 mg/dL with a standard deviation of 35.73 after hemodialysis. Creatinine levels before and after hemodialysis were 13.12 mg/dL (standard deviation: 3.8 mg/dL) and 13.42 mg/dL (standard deviation: 4.65 mg/dL), respectively. This aligns with the study method, where ESRD patients were included, and the efficacy of hemodialysis is consistent with the Bhuvaneswari et al. study in 2023. In Bhuvaneswari's study, mean values of salivary urea and creatinine were significantly increased in the case group compared to the control group, showing a significant decrease post-dialysis. Salivary urea was significantly positively

correlated with serum urea (r-value: 0.366, p-value: 0.009), but no significant correlation was observed between salivary and serum creatinine.[16]

Indoxyl sulfate levels were measured before and after hemodialysis, with the mean before hemodialysis at 47.32 µg/mL (standard deviation: 29.19 µg/mL) and after hemodialysis at 27.81 µg/mL (standard deviation: 21.31 µg/mL). Due to the high prevalence of cardiovascular disease in ESRD patients, the higher accumulation of uremic toxins, including indoxyl sulfate, is thought to be involved in the pathogenesis and progression of ESRD. Indoxyl sulfate levels correlate with the stage of renal failure, and it belongs to the indolic uremic toxin family along with indole-3 acetic acid (IAA). IAA levels have predictive solid power in detecting mortality and cardiovascular events in ESRD, correlating with CRP and malondialdehyde, indicators of inflammation and oxidative stress. However, IAA failed to predict cardiovascular events, mortality, or graft survival in transplant patients.[17] In contrast, serum IS levels were higher in patients with ESRD progression than those without progression in cohort studies with different ESRD stages, strongly associated with renal progression and all-cause mortality, especially in advanced ESRD. [17]

Another finding in this study is the efficacy of hemodialysis in reducing IS, which is consistent with the Hyspler et al. study in 2018. While hemodialysis therapy effectively reduced IS levels, it is noteworthy that IS could not reach normal values, as discussed by Hyspler, suggesting that results are still inadequate.[18]

Our study revealed a correlation between IS levels and patients' functional ability. This finding aligns with various studies, although the Karnofsky scale is novel. A prospective cohort study conducted by Wang et al. demonstrated that serum IS levels were higher in patients with AKI and were associated with all-cause mortality in AKI patients requiring hospitalization. While not clearly verified, the relationship between IS levels and clinical outcomes implicates decreased tubular excretion of IS in the setting of tubular injury and decreased OAT expression in the pathogenesis of IS accumulation during AKI.[17,19] Moreover, a prospective study among hemodialysis patients reported that those with high IS levels had a greater incidence of heart failure compared to the low IS level group, even after adjusting for traditional and uremic-related risk factors. Additionally, serum IS levels predicted restenosis and thrombosis rates of arteriovenous fistulas or arteriovenous grafts in hemodialysis patients undergoing angioplasty, with a median follow-up of 32 months.[17,20]

The limitation of this study lies in its single-center nature. H. Adam Malik Hospital is a tertiary referral hospital attracting patients with intricate and challenging conditions. Conducting multi-center research would offer a more comprehensive understanding of the phenomena observed in the field.

CONCLUSION

Based on the obtained data, the conclusions of this study are as follows: (1) Among the 56 study samples, the mean age was 49.35 years with a standard deviation of 12.3 years, predominantly male, of Batak ethnicity, and in ESRD stage 5. (2) The average indoxyl sulfate level was 47.32 µg/mL, with a standard deviation of 29.19 µg/mL. In general, most patients exhibited functional ability, as calculated by the Karnofsky score, falling into category A, and (3) The Spearman test analysis revealed a moderate negative correlation between indoxyl sulfate levels and the functional ability of patients.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management. JAMA. 2019;322(13):1294.
2. KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney international supplements. 2013 Jan 1;3(1):1-50.
3. Lim YJ, Sidor NA, Tonial NC, Che A, Urquhart BL. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins. 2021 Feb 13;13(2):142.
4. Meyer TW, Hostetter TH. Uremia. New England Journal of Medicine. 2007 Sep 27;357(13):1316-25.
5. Tan X, Cao X, Zou J, Shen B, Zhang X, Liu Z, *et al*. Indoxyl sulfate, a valuable biomarker in chronic kidney disease and dialysis. Hemodialysis International. 2017 Apr;21(2):161-7.
6. Yamamoto S, Fuller DS, Komaba H, Nomura T, Massy ZA, Bieber B, *et al*. Serum total indoxyl sulfate and clinical outcomes in hemodialysis patients: results from the Japan Dialysis Outcomes and Practice Patterns Study. Clinical kidney journal. 2021 Apr;14(4):1236-43.
7. Itoh Y, Ezawa A, Kikuchi K, Tsuruta Y, Niwa T. Protein-bound uremic toxins in hemodialysis patients measured by liquid chromatography/tandem mass spectrometry and their effects on endothelial ROS production. Analytical and bioanalytical chemistry. 2012 Jun;403(7):1841-50.
8. Duranton F, Cohen G, De Smet R, Rodriguez M, Jankowski J, Vanholder R, *et al*. Normal and pathologic concentrations of uremic toxins. Journal of the American Society of Nephrology: JASN. 2012 Jul;23(7):1258.
9. Leong SC, Sirich TL. Indoxyl sulfate-review of toxicity and therapeutic strategies. Toxins. 2016 Nov 30;8(12):358.
10. Hyšpler R, Tichá A, Šafránek R, Moučka P, Nývltová Z, Štochlová K, *et al*. Indoxyl sulfate elimination in renal replacement therapy: influence of citrate-versus acetate-buffering component during bicarbonate dialysis. Disease Markers. 2018 Aug 15;2018.
11. Poluan F, Sugeng C, Surachmanto E. Profil pasien penyakit ginjal kronik yang dirawat di RSUP Prof. Dr. RD Kandou Manado periode Juni 2014-Juli 2015. e-CliniC. 2016 Apr 9;4(1).
12. Harris RC, Zhang MZ. The role of gender disparities in kidney injury. Ann Transl Med. 2020 Apr;8(7):514.
13. Siregar, A. Prevalensi dan Karakteristik Penyakit Ginjal Kronis Stadium 5 yang Menjalani Hemodialisa di RSUP. H. Adam Malik Tahun 2017-2018. Universitas Sumatera Utara. 2019.
14. Suriyong P, Ruengorn C, Shayakul C, Anantachoti P, Kanjanarat P. Prevalence of chronic kidney disease stages 3-5 in low- and middle-income countries in Asia: A systematic review and meta-analysis. PLoS One. 2022 Feb 25;17(2):e0264393.
15. Shaikh H, Hashmi MF, Aeddula NR. Anemia of Chronic Renal Disease. [Updated 2023 Feb 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539871/
16. Nagarajan Bhuvaneswari V, Alexander H, Shenoy MT, D S, Kanakasekaran S, Pradipta Kumar M, et al. Comparison of serum urea, salivary urea, and creatinine levels in pre-dialysis and post-dialysis patients: A case-control study. Cureus. 2023.
17. Cheng TH, Ma MC, Liao MT, Zheng CM, Lu KC, Liao CH, et al. Indoxyl sulfate, a tubular toxin, contributes to the development of chronic kidney disease. Toxins. 2020 Oct 29;12(11):684.
18. Hyšpler, R., Tichá, A., Šafránek, R., Moučka, P., Nývltová, Z., Štochlová, K., Dusilová-Sulková, S. and Zadák, Z., 2018. Indoxyl sulfate elimination in renal replacement therapy: influence of citrate-

versus acetate-buffering component during bicarbonate dialysis. Disease Markers, 2018.
19. Schulman G, Berl T, Beck GJ, Remuzzi G, Ritz E, Arita K, et al. Randomized placebo-controlled EPPIC trials of AST-120 in CKD. Journal of the American Society of Nephrology: JASN. 2015 Jul;26(7):1732.
20. Wang W, Hao G, Pan Y, Ma S, Yang T, Shi P, et al. Serum indoxyl sulfate is associated with mortality in hospital-acquired acute kidney injury: A prospective cohort study. BMC nephrology. 2019 Dec;20(1):1-1.

How to cite this article: M. Ikhsan Fadillah, Syafrizal Nasution, Sumi Ramadani. The relationship between indoxyl sulfate levels and functional ability of end-stage renal disease patients undergoing regular haemodialysis using the Karnofsky scale measuring instrument at Haji Adam Malik Central General Hospital Medan. *International Journal of Research and Review*. 2023; 10(12): 731-739. DOI: *https://doi.org/10.52403/ijrr.20231273*

******