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Editorial

Contemporary Issues in Kidney Disease: Addressing Acute Kidney Injury and Inflammation
Pringgodigdo Nugroho

Original Article

Correlation Between RET-He and Quality of Life in Chronic Kidney Disease Patients with Routine Hemodialysis: A Study at Ulin General Hospital Banjarmasin
Adlan Fariz, Mohammad Rudiansyah, Enita Rakhmawati Kurniaatmaja, et al.

Acute Kidney Injury Incidence in COVID-19 Patients Receiving Remdesivir Therapy at Awal Bros Panam Hospital
Ade Novita Reslina, Faradilla Monita, Ligat Pribadi Sembiring

Vitamin D Insufficiency with Elevated ADMA and hs-CRP: A Single-center Study of Chronic Kidney Disease Patients Undergoing Hemodialysis
Lusito Lusito, Lestariningsih Lestariningsih, Dwi Lestari Partiningrum, et al.

Estimated Glomerular Filtration Rate and Sleep Quality in Stage 3-5 Non-Dialysis Chronic Kidney Disease Patients: Is There a Correlation?
Octavianus Umboh, Stella Palar, Emma Syarifih Moeis

Review Article

A Review of Central Vein Catheter for Hemodialysis: Insertion Sites and Techniques
Jefri Pratama Susanto, Achmad Rifai

Case Report

Severe Clinical Impact of Multiple Wasp Stings: A Case Report of Acute Kidney Injury
Hana Fauziyah, Bayu Rusfandi Nasution, Alwi Thamrin Nasution

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TABLE OF CONTENT

EDITORIAL

CONTEMPORARY ISSUES IN KIDNEY DISEASE: ADDRESSING ACUTE KIDNEY INJURY AND INFLAMMATION 1
Pringgodigdo Nugroho

ORIGINAL ARTICLE

CORRELATION BETWEEN RET-HE AND QUALITY OF LIFE IN CHRONIC KIDNEY DISEASE PATIENTS WITH ROUTINE HEMODIALYSIS: A STUDY AT ULIN GENERAL HOSPITAL BANJARMASIN 5
Adlan Fariz, Mohammad Rudiansyah, Enita Rakhmawati Kurniaatmaja, Nanik Tri Wulandari, Dewi Indah Noviana Pratiwi

ACUTE KIDNEY INJURY INCIDENCE IN COVID-19 PATIENTS RECEIVING REMDESIVIR THERAPY AT AWAL BROS PANAM HOSPITAL 12
Ade Novita Reslina, Faradilla Monita, Ligat Pribadi Sembiring

VITAMIN D INSUFFICIENCY WITH ELEVATED ADMA AND HS-CRP: A SINGLE CENTER STUDY OF CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HEMODIALYSIS 20
Lusito Lusito, Lestariningsih Lestariningsih, Dwi Lestari Partiningrum, Shofa Chasani, Arwedi Arwanto, Ayudyah Nurani, Fadhli Rizal Makarim

ESTIMATED GLOMERULAR FILTRATION RATE AND SLEEP QUALITY IN STAGE 3-5 NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS: IS THERE A CORRELATION? 28
Octavianus Umboh, Stella Palar, Emma Syarifih Moeis

REVIEW ARTICLE

A REVIEW OF CENTRAL VEIN CATHETER FOR HEMODIALYSIS: INSERTION SITES AND TECHNIQUES 33
Jefri Pratama Susanto, Achmad Rifai

CASE REPORT

SEVERE CLINICAL IMPACT OF MULTIPLE WASP STINGS: A CASE REPORT OF ACUTE KIDNEY INJURY 45
Hana Fauziyah, Bayu Rusfandi Nasution, Alwi Thamrin Nasution

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Editorial

Contemporary Issues in Kidney Disease: Addressing Acute Kidney Injury and Inflammation

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Acute Kidney Injury

Acute kidney injury (AKI) is marked by a rapid decrease in kidney function, typically occurring over a few hours to several days. This leads to the retention of metabolic waste products and the disruption in electrolyte, fluid, and acid-base homeostasis.[1] It is a multifaceted syndrome characterized by high rates of morbidity and mortality, precipitating short-term adverse outcomes and posing a significant risk for cardiovascular events, kidney cancer, and chronic kidney disease (CKD), among survivors. Furthermore, the incidence of COVID-19-related AKI has been notably high, as reported by Reslina et al., mirroring the global pandemic.[2] In addition to the rising number of COVID-19-related acute kidney injuries (AKI), wasp stings (Fauziyah et al.) and snake bites are also becoming increasingly common causes worldwide.[3] Consequently, AKI profoundly impacts the quality of life for survivors and imposes substantial burdens on healthcare system.[2]

At present, diagnosing AKI remains challenging. Firstly, in its early stages, AKI can be asymptomatic because clinical signs are largely dependent on the degree of renal impairment. Secondly, the glomerular filtration rate (GFR) is a key indicator for evaluating renal function; however, no tools are available for real-time monitoring of GFR. In clinical practice, urine volume and serum creatinine levels are employed to assess changes in GFR, but they are neither sensitive nor specific.[2]

Managing AKI clinically is also challenging because of its complex pathophysiological mechanisms, influenced by various comorbidities and etiologies. The primary goal of managing AKI is to address the underlying causes of the condition and prevent further kidney damage. However, identifying these causes can be complex and may not be recognized by clinicians until it is too late, resulting in potential kidney damage. Unfortunately, no specific pharmacological approach is available at this time. Additionally, patients with AKI may experience various complications, including imbalances in electrolyte, fluid, and acid-base levels. Consequently, the primary clinical strategies employed in managing AKI are symptomatic and supportive therapies. Fluid management plays a crucial role in both preventing and treating AKI.[4] In cases of severe AKI, renal replacement therapy

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(RRT) becomes necessary and can be life-saving. The most accurate indicators for initiating RRT include volume overload, metabolic acidosis, refractory hyperkalemia, or signs of uremia. However, there is considerable debate over the best timing to initiate RRT in patients who do not have severe complications.[5] Additionally, ongoing discussions center around whether continuous or intermittent RRT is preferable and the appropriate timing for discontinuing RRT.[6, 7]

From a therapeutic standpoint, RRT with extracorporeal hemoadsorption can remove inflammatory mediators, expanding its role beyond just maintaining fluid and electrolyte balance. While the pathogenesis of acute kidney injury (AKI) remains not fully understood, immune response dysregulation is believed to be one of the pathological mechanisms underlying sepsis and COVID-19-associated AKI. In theory, early removal of inflammatory mediators can help restore immune balance, alleviating the severe systemic effects of infection.[8] Additionally, decreased renal perfusion is widely recognized as a leading mechanism in most cases of AKI. This leads to renal ischemia and hypoxia, increasing reactive oxygen species (ROS). Substantial evidence revealed that AKI is associated with increased ROS and decreased antioxidants.[9] Therefore, targeting excessive ROS may represent a new and specific approach to treating AKI.

Inflammation

This AKI can lead to the development of CKD in many patients. Numerous studies show that AKI is a significant risk factor for progressing to CKD and end-stage renal disease (ESRD).[10-12] AKI presents a wide range of clinical scenarios, from mild to severe injury, with the potential to lead to permanent and complete loss of renal function.[13] Patient with AKI should be closely monitored for the development of new CKD or progression of underlying CKD.[11] Mechanism of progression from AKI to CKD include subclinical inflammation leading to persistent structural and functional changes within the kidneys, impaired renal regenerative capacity resulting in maladaptive repair, and vascular and tubular injury causing reduced blood flow and impaired kidney function.[10] Progression of CKD can result in ESRD, which necessitates definitive treatment options such as dialysis or kidney transplantation to sustain life. Hemodialysis is one of the most prevalent kidney replacement therapies worldwide, as it allows for removing waste products, excess fluids, and electrolyte imbalances that accumulate in patients with kidney failure.[14] Outcome of maintenance hemodialysis patients remains poor with high morbidity and mortality. Patients on dialysis have a significantly reduced life expectancy compared to the general population of the same age and sex.[13] One of the most important factors for survival on dialysis is the presence of cardiovascular comorbidities with an underlying high inflammation state.[15]

Inflammation in hemodialysis patients likely stems from uremia and the dialysis procedure. Oxidative stress, accumulation of uremic toxins, and bioincompatibility of dialysis membranes all contribute to the inflammatory state. Several inflammation markers, like C-reactive protein, Interleukin-6, and Tumor Necrosis Factor-alpha, are often elevated in dialysis patients. While there are many inflammatory markers associated with negative outcomes in hemodialysis patients, such as C-reactive protein, Interleukin-6, and Tumor Necrosis Factor-alpha, research suggests that high-sensitivity C-reactive protein (hs-CRP) is a strong predictor of mortality and other complications in these patients.[16] It is essential to highlight that while hs-CRP serves as a strong predictor, it is not the sole determinant of patient outcomes. Other factors, including the patient's overall health status, comorbidities, and treatment adherence, also play significant roles. Another important consideration is the role of asymmetric dimethylarginine (ADMA) in hemodialysis patients. ADMA is an endogenous inhibitor of nitric oxide synthase, and elevated levels of ADMA are associated with higher cardiovascular risk and increased mortality in this population.[17]

ADMA is an important factor linked to increased inflammation and poorer outcomes in hemodialysis patients. Studies have demonstrated that ADMA levels are significantly higher in hemodialysis patients compared to healthy individuals. The increase in ADMA is thought to be due to decreased renal clearance and increased oxidative stress and inflammation associated with the hemodialysis procedure. This increase causes impairment of nitric oxide production, which can lead to endothelial dysfunction, increased vascular resistance, and, ultimately, cardiovascular complications.[18]

Many studies have linked ADMA with other factors. One of the factors is vitamin D deficiency in hemodialysis patients, which is associated with increased inflammation and higher mortality.[17, 19] Prevalence vitamin D deficiency is very high in the CKD and dialysis population. A prevalence rate of 80-90% has been reported. The mechanism by which vitamin D deficiency can lead to heightened inflammation involves its role in regulating the immune system. Vitamin D has anti-inflammatory properties and its deficiency is associated with increased inflammatory cytokine production.[20] Lusito et al. study found a correlation of vitamin D deficiency with ADMA in hemodialysis patients.

Kidney disease is a multifaceted and complex condition that poses significant challenges in modern healthcare. Addressing AKI and inflammation stands out as particularly critical among the various contemporary issues in kidney disease. AKI, a sudden loss of kidney function that can arise from a multitude of causes, demands prompt and effective management to prevent long-term damage. Additionally, inflammation, a key driver of CKD progression, necessitates targeted therapeutic strategies to mitigate its harmful effects. These interconnected issues underscore the need for innovative solutions and comprehensive care approaches to improve patients' lives with kidney disease.

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Original Article

Correlation Between RET-He and Quality of Life in Chronic Kidney Disease Patients with Routine Hemodialysis: A Study at Ulin General Hospital Banjarmasin

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ABSTRACT

Background: The 2018 Riskesdas report revealed that the incidence of chronic kidney disease (CKD) affects 0.38% of Indonesia's population. Anemia frequently complicates CKD, especially in patients undergoing regular hemodialysis. Reticulocyte hemoglobin equivalent (RET-He) assesses hemoglobin content in reticulocytes, indicating iron availability for erythropoiesis in the bone marrow. CKD significantly impacts patients' socio-economic status, heightening morbidity and mortality while diminishing quality of life. The relationship between RET-He and the quality of life in CKD patients on routine hemodialysis remains unclear.

Objective: To investigate the correlation between RET-He and quality of life in CKD patients undergoing routine hemodialysis.

Methods: A cross-sectional observational analytical study with data from medical records of CKD patients receiving routine hemodialysis between October 1st and October 30th, 2021. The Spearman correlation test was used for analysis.

Results: This study included 92 patients, consisting of 40 males and 52 females, with a median age of 50 years and RET-He values at 31. Quality of life metrics included physical function (800, range: 0-1000), physical limitations (300, range: 0-400), body pain (175, range: 75-255), general health (475, range: 225-600), vitality (320, range: 200-400), social function (175, range: 75-200), emotional limitations (300, range: 100-300), and mental health (380, range: 160-500). The correlation analysis revealed no significant relationships: physical function (p=0.359), physical limitations (p=0.813), body pain (p=0.373), general health (p=0.547), vitality (p=0.616), social function (p=0.828), emotional limitations (p=0.482), and mental health (p=0.136).

Conclusion: There is no significant correlation between RET-He levels and the quality of life in CKD patients undergoing regular hemodialysis.

Keywords: RET-He, chronic kidney disease, quality of life.

Introduction

Chronic Kidney Disease (CKD) continues to pose a significant challenge in the medical field. Approximately 80% of CKD patients live in countries with large elderly populations and readily accessible healthcare systems.[1] The 2018 Riskesdas report indicated an increase in non-communicable diseases, including stroke, cancer, diabetes mellitus, chronic kidney disease, and hypertension,

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compared to the 2013 data. In Indonesia, CKD affects 0.38% of the population, amounting to 713,783 individuals out of 252,124,458.[2, 3]

Anemia is prevalent among CKD patients, particularly those undergoing routine hemodialysis. This condition is primarily due to inadequate endogenous erythropoietin production, with iron deficiency also playing a significant role.[4] In these patients, iron deficiency can result from gastrointestinal bleeding, blood retention in the dialysis circuit, requent blood draws, and malnutrition. Poor dietary intake, absorption issues, and the use of anticoagulants further increase the risk of bleeding. Chronic blood loss within the dialysis circuit and frequent blood tests further deplete iron levels. Functional iron deficiency may also occur when inflammation or other factors impair the use of iron for red blood cell production, even if total body iron levels are normal. Managing this involves regular monitoring of iron status, nutritional support, minimizing blood loss, and optimizing iron therapy.[5]

Various biochemical markers, including serum ferritin, serum transferrin saturation (TSAT), percentage of hypochromic erythrocytes (%HYPO), reticulocyte hemoglobin content (CHr), erythrocyte zinc protoporphyrin (Er-ZPP), and reticulocyte hemoglobin equivalent (RET-He), are used to diagnose iron deficiency anemia (IDA) in CKD patients. Serum ferritin reflects iron stores, TSAT measures iron availability, %HYPO indicates hypochromic erythrocytes, CHr assesses hemoglobin content in reticulocytes, Er-ZPP levels reflect decreased iron availability for heme synthesis, and RET-He evaluates iron-restricted erythropoiesis. These markers, often used together, help clinicians assess iron status, considering factors like inflammation and erythropoiesis-stimulating agents that can affect individual marker interpretation.[6]

RET-He measures the hemoglobin content in reticulocytes, providing insight into iron availability for erythropoiesis in the bone marrow. Reticulocytes, being less mature than erythrocytes, circulate more rapidly and can be more sensitive indicators of ongoing erythropoietic activity. This sensitivity makes RET-He a valuable marker for assessing iron status and erythropoietic activity, particularly in CKD, where anemia is prevalent and monitoring iron levels is crucial for effective management.[7, 8] Given the challenges in accurately assessing iron status in this population, particularly with confounding factors such as inflammation and erythropoiesis-stimulating agents, RET-He is a valuable tool for diagnosing and managing IDA in hemodialysis patients. Integrating RET-He into routine clinical practice could streamline monitoring efforts and enhance treatment strategies for anemia in this population.[5, 7, 9]

CKD significantly affects patients both medically and socio-economically, leading to decreased quality of life and increased morbidity and mortality rates. The disease often necessitates frequent medical visits, treatments such as dialysis or kidney transplantation, and medications, imposing a financial burden on patients and their families. Additionally, CKD may cause complications such as cardiovascular disease, anemia, bone disease, and neurological issues, further diminishing patients' overall well-being and functionality. CKD can also impair their ability to work, resulting in potential loss of income and disruption of social and professional lives. Addressing the socio-economic impacts of CKD is crucial for comprehensive care, improving patient outcomes, and enhancing quality of life.[1, 10, 11]

A patient's quality of life is a multidimensional concept encompassing physical health, mental status, independence, social relationships, and environmental confidence. It reflects their overall perception of their life situation, including their goals, hopes, standards, and concerns. In CKD, maintaining or improving quality of life is a key treatment goal. This involves managing physical symptoms and complications while addressing psychosocial and environmental factors affecting the well-being of the patients.[12]

Research on the relationship between RET-He levels and quality of life among CKD

patients undergoing routine hemodialysis remains limited. Previous studies have highlighted RET-He as a promising alternative parameter for diagnosing IDA in routine hemodialysis patients. This study aims to provide valuable insights into how RET-He, a marker of iron availability for erythropoiesis, may impact the overall well-being and quality of life of CKD patients receiving hemodialysis. The expected benefit of this research lies in enhancing our understanding of the relationship between RET-He and quality of life, providing clinicians with additional insights for better assessment and management of anemia in CKD patients undergoing routine hemodialysis. By elucidating this correlation, healthcare providers could be better equipped to tailor treatment strategies, improving both hematologic status and quality of life for these patients.

Methods

Design and participants

This study is a non-experimental analytical observational study utilizing a cross-sectional approach. It was conducted at the hemodialysis unit at Banjarmasin Ulin General Hospital from October 1st to October 30th, 2021, focusing on CKD patients undergoing routine hemodialysis. The participants were selected using non-probability sampling, specifically consecutive sampling, where individuals are enrolled sequentially as they become available. The minimum sample size was set at 74 patients, allowing for the inclusion of CKD patients receiving hemodialysis treatment during the study period. The objective was to analyze the relationship between RET-He levels and the quality of life in this patient population, providing valuable insights into their health status and well-being.

The final sample comprised 92 patients who met the inclusion criteria: diagnosed with CKD, aged between 18 and 65 years, and undergoing routine hemodialysis for more than 3 months with a frequency of two sessions per week. The exclusion criteria are incomplete medical records, current hospitalization, acute infection confirmed by physical examination, malignant disease, ongoing immunosuppressant or steroid therapy, use of non-steroidal anti-inflammatory drugs (NSAIDs), and autoimmune conditions. Data were obtained from medical records and included demographic information (gender, age), hemodialysis duration, and RET-He levels. The RET-He variable is numerical. Quality of life data were obtained through the Short Form-36 (SF-36) questionnaire, which measures mental health, emotional limitations, social function, vitality, general health, body pain, physical limitations, and physical function. The quality of life variable is also numerical.

Table 1. Research variable

Variable Name	Definition	Measurement Procedure	Measurement Results	Data Scale
RET-He	Iron content in reticulocytes in the blood circulation.[7]	Obtained from patient biochemical data	The amount of iron in the patient's reticulocytes	Numerical
Quality of life of CKD patients	CKD patient's perception of their position in life, goals, hopes, standards, and concerns.[12]	Completed SF-36 questionnaire	Numerical values describing various aspects including mental health, emotional limitations, social function, vitality, general health, body pain, physical limitations, and physical function	Numerical

Statistical analysis

Statistical data analysis was performed using SPSS software. Descriptive analysis was computed to summarize basic patient characteristics. The Kolmogorov-Smirnov normality test was used to assess the normality of

distributions for patient age, RET-He levels, and SF-36 subscales. The Pearson correlation test was used to assess correlation when both datasets were normally distributed, and the Spearman correlation test was used when the datasets were not normally distributed. Significance was defined based on a p-value of <0.05.

Results

The study included 92 subjects, with 40 males and 52 females. Data on the age of CKD patients undergoing routine hemodialysis range between 16 and 65 years (Table 2).

Table 2. Profile of research subjects

Variable Name	N	Min-Max	Mean	Standard deviation
Age	92	16 – 65	49.01	10,833
RET-He	92	20 – 37	31.09	3,434
Physical function	92	0 – 1000	741.30	214,400
Physical limitations	92	0 – 400	287.77	81,999
Body aches	92	75 – 255	167.01	36,847
General health	92	225 – 600	448.10	104,055
Vitality	92	200 – 400	302.83	56,846
Social function	92	75 – 200	164.73	34,580
Emotional limitations	92	100 – 300	255.43	54,196
Mental function	92	160 – 500	371.25	92,545

A data normality test was carried out using the Kolmogorov-Smirnov method. It was found that data on patient age, RET-He, mental health, emotional limitations, social function, vitality, general health, body pain, physical limitations, and physical function were not normally distributed, requiring the use of the Spearman correlation test for these variables (Table 3).

Table 3. Kolmogorov-Smirnov normality test results

Variable Name	Statistics	DF	SIG.
Age	0,097	92	0,031
RET-He	0,137	92	0,000
Physical function	0,201	92	0,000
Physical limitations	0,298	92	0,000
Body aches	0,217	92	0,000
General health	0,119	92	0,003
Vitality	0,195	92	0,000
Social function	0,205	92	0,000
Emotional limitations	0,371	92	0,000
Mental function	0,115	92	0,005

The data were analyzed using the Spearman correlation test to determine their significance. It was found that RET-He did not affect the patient's quality of life as described by mental health, emotional limitations, social function, vitality, general health, body pain, physical limitations, and physical function ($p>0.05$) (Table 4).

Table 4. Spearman correlation test results

	RET-HE	
	P VALUE	R
Physical function	0,359	-0,097
Physical limitations	0,813	-0,025
Body aches	0,373	-0,094
General health	0,547	-0,064
Vitality	0,616	0,053
Social function	0,828	0,023
Emotional limitations	0,482	-0,074
Mental function	0,136	-0,157

Discussion

Health-related quality of life is known to be reduced in patients with CKD, with anemia often exacerbating this decline. RET-He measures the iron content in reticulocytes, young red blood cells, and provides a more accurate reflection of iron availability over the 120-day lifespan of erythrocytes. This study examined the relationship between RET-He and quality of life in CKD patients undergoing routine hemodialysis. The Spearman correlation test was used for this analysis, but the results revealed no significant relationship between these variables. Although low RET-He values can indicate iron deficiency in CKD patients with anemia and potentially worsen their overall condition, our study found that low RET-He levels did not affect their quality of life. This outcome may be influenced by factors such as the duration of hemodialysis, the patient's age, comorbidities, and the environmental support.

In contrast to our findings, a study by Krishnan et al. in 2020 reported that about two-thirds (68%) of CKD patients undergoing routine hemodialysis experienced a decline in their quality of life compared to those who had undergone kidney transplantation.[13] This is consistent with Pretto et al., who identified common causes for reduced quality of life in these patients, including symptoms of depression, complications such as recurrent infections, headaches, pain, anemia, and post-hemodialysis fatigue.[14] The differences between these studies and our research could be due to variations in sample size, with larger samples potentially including patients with longer histories of hemodialysis and more complex complications.

The SF-36, used to assess the quality of life in CKD patients, includes measures of mental health, emotional limitations, social function, vitality, general health, body pain, physical limitations, and physical function. Several studies have reported a high prevalence of depression among CKD patients, negatively impacting their mental health. Depression in CKD patients is often linked to poor clinical conditions, comorbidities, complications from the disease and its treatment, and prolonged hospital stays.[15, 16] A 2018 study by Souweine et al. highlighted that post-dialysis weakness could also affect physical function, associated with protein-energy wasting, and reduced physical activity.[17]

Research from Iran has shown a significant positive association between medication adherence and overall quality of life scores. This highlights the importance of personalized educational interventions to enhance patients' understanding of their condition and the importance of treatment adherence.[18] The study concluded that failing to adhere to treatment properly would increase the perception of disease symptoms and negatively impact the patient's physical function, psycho-emotional limitations, and social function. These studies did not find a significant correlation between RET-He and patients' physical function, emotional limitations, or social function, possibly due to some patients already being well-informed about their condition and adhering to treatment.

In this study, the non-significant relationship between RET-He and quality of life suggests that anemia and other CKD complications can contribute to deteriorating kidney function. Observational data can make it challenging to disentangle the specific impact of anemia from other influencing factors. However, data from larger patent cohorts with multiple variables could offer deeper insights. This research indicates that the quality of life of CKD patients is not solely determined by RET-He levels, which describe the patient's iron deficiency anemia. The patient's condition is multifaceted and influenced by various factors, such as age, duration of hemodialysis, complications from diseases and treatments, individual comorbidities, and environmental support. Addressing iron deficiency anemia in CKD patients through appropriate therapy can improve their condition and reduce complications associated with CKD. Comprehensive patient care, including education for patients and their families, is crucial for maintaining quality of life and preserving mental health. Therefore, multiple factors must be addressed to improve and maintain the quality of life for CKD patients.

Conclusion

The study found no significant relationship between RET-He and the quality of life in CKD patients undergoing routine hemodialysis. Various factors, including the patient's age, the duration of hemodialysis treatment, individual disease and treatment complications, diverse comorbidities, and environmental support, likely influence this outcome.

Limitations of the Study

Several confounding factors not examined in this research could have impacted the results. Further research is needed to better understand the relationship between RET-He and quality of life in CKD patients undergoing routine hemodialysis.

Declarations

Ethics approval and consent to participate

This study adhered to all ethical guidelines set forth by the research site.

Competing interests

The authors declare no conflict of interest related to this article. The research and results are presented impartially and objectively.

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Author's Contribution

Idea/concept: MR, RK. Design: MR. Control/supervision: TW, NP. Data collection/processing: AF. Analysis/interpretation: AF. Literature review: AF, NP, TW, RK. Writing the article: AF, MR, RK, Critical review: MR, RK. 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

Acute Kidney Injury Incidence in COVID-19 Patients Receiving Remdesivir Therapy at Awal Bros Panam Hospital

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ABSTRACT

Background: Remdesivir is one of the pharmacological therapies for moderate COVID-19 patients. Remdesivir is an antiviral that can increase the risk of nephrotoxicity.
Objective: The study aims to evaluate the incidence of acute kidney injury (AKI) in COVID-19 patients receiving remdesivir.
Methods: This is a cross-sectional analytic study of 238 COVID-19 patients receiving remdesivir therapy at Awal Bros Panam Hospital for the period 2020–2022. AKI was diagnosed using the KDIGO criteria. The chi-square test was used to determine the correlation of AKI incidence with age, gender, and comorbidities, with a significance level of $p < 0.05$.
Results: AKI was found in 32 patients (13.4%). The majority of AKI patients (75%) were aged 60 years or older, with 65.6% being male. Additionally, 84.4% of these patients had comorbidities, and 53.1% of them died. Around half of the patients were diagnosed with stage 1 AKI, and the majority, specifically 84.4%, did not undergo renal replacement therapy (RRT). The association between the incidence of AKI and age and comorbidities was shown to be statistically significant (p=0.000; RR 5.11; 95% CI 2.44-10.8 and p=0.009; RR 3.05; 95% CI 1.22-7.64, respectively).
Conclusion: The main risk factors for AKI are primarily observed in the older population and individuals with several medical conditions. Greater emphasis should be placed on administering remdesivir to COVID-19 patients who are elderly and have comorbidities, as they are at a higher risk of developing AKI.
Keywords: acute kidney injury, COVID-19, remdesivir, KDIGO.

Introduction

Acute kidney injury (AKI) refers to a deviation from normal kidney structure and function that is identified within 48 hours using blood, urine, tissue, or radiological tests.[1] AKI is a rapid deterioration in kidney function in previously healthy kidneys, sometimes necessitating dialysis treatment.[2] It is associated with a rise in death rates and the risk of developing chronic kidney disease (CKD).[3]

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus.[4] The lungs are the primary organ affected by COVID-19. However, other organs such as the kidneys and liver are also implicated. The majority of the medications administered to individuals with COVID-19 are eliminated from the body through the renal system. Hence, alterations in kidney function can significantly affect the levels of medication in the body as a result of poor elimination and breakdown, which may result in either harmful effects or diminished effectiveness.[5]

According to the World Health Organization, from December 31, 2019 to July 30, 2023, there were 768,633,601 confirmed cases

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of COVID-19, resulting in 6,953,107 deaths. The case fatality rate (CFR) was 0.90%.[4] As of July 2023, Indonesia has recorded a total of 6,812,949 confirmed cases of COVID-19, with 161,909 deaths (CFR = 2.38%) and 6,646,181 recoveries. These cases are distributed throughout 34 provinces.[6] Riau Province has recorded a total of 154,874 confirmed cases of COVID-19, with 150,280 individuals having recovered from the virus. Pekanbaru City has the highest number of confirmed COVID-19 cases in the province of Riau, with a total of 65,371 cases. Additionally, there have been 63,936 recoveries in the city.[7] Awal Bros Panam Hospital recorded a cumulative total of 4,938 confirmed cases of COVID-19 between 2020 and 2022, including both outpatients and inpatients.[8]

Within the COVID-19 management protocol, patients with moderate and severe symptoms are treated with pharmacological therapy, which includes the administration of antiviral drugs. One of the options for antiviral treatment is remdesivir.[9] Other options include nirmatrelvir with ritonavir (paxlovid), azvudine, molnupiravir, oseltamivir, famsiclovir, and favipiravir.[10] Apart from COVID-19, remdesivir is a broad-spectrum antiviral medication that has demonstrated its effectiveness against various viruses.[11] To monitor potential kidney damage, it is crucial to monitor the glomerular filtration rate (GFR) in COVID-19 patients who are being treated with remdesivir. Remdesivir treatment is discontinued when the GFR decreases to 50% of the initial level. The frequency of AKI in COVID-19 patients receiving remdesivir medication is exacerbated by several risk variables, including age, gender, and concomitant disorders.[12] The antivirals that are safe to use in kidney impairment include azvudine, molnupiravir, nirmatrelvir with ritonavir (Paxlovid), and oseltamivir and famsiclovir, which are now undergoing clinical trials.[10]

A study in Tiongkok in 2020 of 20 patients with mild-moderate COVID-19 with azvudine therapy showed no kidney-related side effects, and in other studies, kidney function parameters were found to be normal.[13, 14] A study conducted in Hong Kong involving 860 COVID-19 patients who received remdesivir treatment while hospitalized indicated that the occurrence of AKI was 15.9%.[15] A study conducted in Brazil indicated that out of the 2,922 cases of remdesivir use in COVID-19 patients, 493 cases (16.9%) were associated with renal and urinary tract diseases. The most common disorder observed was AKI, which occurred in 338 cases (11.6%).[16]

Currently, there is a scarcity of data on the occurrence of AKI in COVID-19 patients undergoing remdesivir therapy in Indonesia. Hence, the objective of this study is to determine the occurrence rate of AKI in COVID-19 patients who are undergoing remdesivir treatment at Awal Bros Panam Hospital.

Methods

Design and participants

This is a cross-sectional study. Data was taken from the medical records of Remdesivir-treated COVID-19 patients at Awal Bros Panam Hospital from November 2020 to December 2022 and analyzed. Inclusion criteria are PCR-diagnosed COVID-19 individuals over 18 years old who received remdesivir were the study subjects. Exclusion criteria are patients with a GFR < 30ml/min/1.73m2, regular hemodialysis patients, and incomplete medical records were removed. Total sampling was used as the sample method for subjects who satisfied the inclusion and exclusion criteria. This study measures age, gender, comorbidities, AKI stage, renal replacement therapy (RRT), and patient outcomes. The study ran from June to September 2023.

According to KDIGO 2012, AKI is defined as a rise in serum creatinine of 0.3 mg/dl within 48 hours, ≥1.5 times from baseline within 7 days, or urine volume below 0.5 ml/kgBB/hour for 6 hours. The creatinine baseline was the mean level measured 7–365 days preceding hospitalization, or the lowest level measured in the hospital. Stage 1 was defined as an increase in serum creatinine of 0.3 mg/dl within 48 hours or 1.5–1.9 times from baseline within 7 days; stage 2 was an increase of 2–2.9 times from baseline; and stage 3 was an increase of 3 times or more from

baseline or an increase > 4 mg/dl or the start of RRT.[17]

COVID-19 patients receiving remdesivir therapy were categorized as adults aged 18–59 and geriatrics aged ≥ 60. Patient genders are male and female. Remdesivir-treated COVID-19 patients have pre-COVID-19 comorbidities such as hypertension, diabetes, and heart disease. AKI treatment includes hemodialysis and conservative therapy. COVID-19 patients with remdesivir therapy have a life-or-death outcome after hospitalization.

Statistical analysis

Demographic data were also reported. Numeric variables were reported as mean and standard deviation, and categorical variables were reported as percentages. Bivariate analysis was performed using an unpaired t-test and a chi-square test. Statistical significance was set at $p < 0.05$. Researchers calculated the relative risk (RR) and 95% confidence interval to determine how age, sex, and comorbidities affected AKI incidence. All analyses were performed using SPSS version 25.0 for Windows (SPSS, Inc.).

Results

During the period November 2020 to December 2022, there were 1,620 COVID-19 patients hospitalized at Awal Bros Panam Hospital. A total of 389 patients received remdesivir therapy. However, 151 patients were excluded because 4 patients were < 18 years old, 7 patients underwent routine hemodialysis, and 140 data were incomplete. This study had 238 patients in total.

According to this study, 13.4% of COVID-19 patients receiving remdesivir medication experienced an incidence of AKI (Figure 1). Table 1 indicates that 75 percent of the 32 patients who experienced AKI belonged to the age group of 60 years or older. The gender of most AKI patients is male, at 65.6%. In patients with comorbidities, the incidence of AKI is higher at 84.4%. The population of AKI patients who died was 53.1%, while the living population was 46.9%. AKI patients based on KDIGO criteria are dominated by stage 1 AKI, which is 50%. Furthermore, only 5 patients (15.6%) out of the 32 AKI patients underwent RRT.

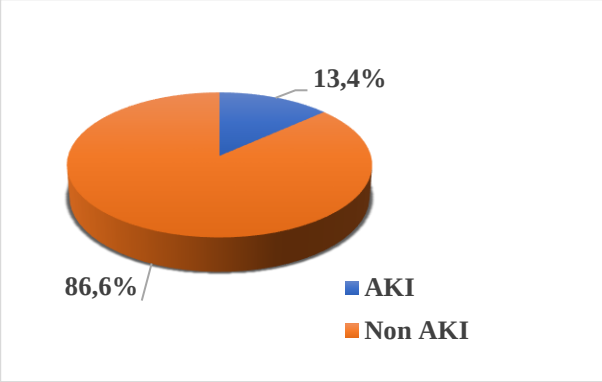

Figure 1. Distribution of COVID-19 patients with remdesivir therapy

Table 1. Characteristics of COVID-19 patients receiving remdesivir therapy

Variable	AKI n (%)	Non-AKI n (%)
Age (years)		
≥ 60	24 (75)	64 (31,1)
18-59	8 (25)	142 (68,9)
Gender		
Male	21 (65,6)	110 (53,4)
Female	11 (34,4)	96 (46,6)
Comorbid condition	27 (84,4)	125 (60,7)
Yes	5 (15,6)	81 (39,3)
No		
Patient Outcome		
Discharge	15 (46,9)	189 (91,7)
Deceased	17 (53,1)	17 (8,3)
AKI Stage (KDIGO)	16 (50)	
Stage 1	7 (21,9)	
Stage 2	9 (28,1)	
Stage 3		
RRT Requirement	5 (15,6)	
HD	27 (84,4)	
No need for RRT		

RRT*: renal replacement therapy*

In COVID-19 patients who were 60 years of age or older and received remdesivir, the incidence of AKI was found to be 27.3%, while at the age of 18–59 years, the incidence of AKI was only 5.3%. Remdesivir-treated male COVID-19 patients had an AKI incidence of

16%, not much different from female patients with an AKI incidence of 10.3%. For COVID-19 patients with comorbidities who get remdesivir, the incidence of AKI is found to be 17.8%, while patients without comorbid AKI incidence is only 5.8%.

Based on the results of the analysis using the chi-square test, there was a significant relationship ($p < 0.05$) between patient age and comorbidities and the incidence of AKI Patient age ≥ 60 years has a relative risk of AKI 5.11 times compared to age 18–59 years. Patients with comorbidities had a relative risk of AKI 3.05 times compared to those without comorbidities, With a p value > 0.05, there was no statistically significant correlation found between the gender variable and the frequency of AKI (Table 2).

Table 2. Correlation of AKI incidence with age, gender, and comorbidities

Variable	AKI n (%)	Non-AKI n (%)	Total n (%)	P	RR	CI (95%)
Age (years)						
≥ 60	24 (27,3)	64 (72,7)	88 (100)			
18-59	8 (5,3)	142 (94,7)	150 (100)	0,000	5,11	2,40−10,8
Gender						
Male	21 (16)	110 (84)	131 (100)			
Female	11 (10,3)	96 (89,7)	107 (100)	0,196	1,55	0,78−3,08
Comorbid condition						
Yes	27 (17,8)	125 (82,2)	152 (100)			
No	5 (5,8)	81 (94,2)	86 (100)	0,009	3,05	1,22−7,64

Discussion

This study found that the administration of remdesivir to patients with COVID-19 resulted in a 13.4% incidence of AKI. Remdesivir binds to the RNA chain of SARS-CoV-2 and functions as an adenosine triphosphate (ATP) analog. As a result, during viral RNA replication, the RNA chain synthesis process is terminated and the RNA-dependent RNA polymerase (RdRp) enzyme is inhibited.[18] Remdesivir has limited aqueous solubility; therefore, sulfobutylether-beta-cyclodextrin sodium (SBECD) is added to the formulation as a solubility-enhancing agent. SBECD is filtered and excreted by the kidneys, so patients with renal impairment are at risk of SBECD accumulation and an increased risk of nephrotoxicity.[19] Remdesivir is effective against a variety of viruses in addition to COVID-19, including filoviruses (like Ebola and Marburg), coronaviruses (like SARS-CoV and MERS-CoV), paramyxoviruses (like parainfluenza type III, Nipah, Hendra, measles, and mumps), and Pnemoviridae.[11]

Wu's (2021) study showed a substantial correlation between the administration of remdesivir and the occurrence of AKI in individuals with COVID-19. Remdesivir had a 2.81-fold higher likelihood of causing AKI compared to alternative drugs considered the main treatment. The mean time until the development of AKI in the remdesivir group was 4.91 ± 7.25 days.[20]

In Sham's study conducted in 2023, it was found that there was no correlation between the use of remdesivir therapy and the risk of AKI. The AKI occurrences mentioned are likely to be complications arising from COVID-19. Although the condition is typically recognized as a respiratory infection, it can also sporadically lead to multi-system disease, impacting other body systems, including the kidneys. Multiple investigations have shown a clear connection between COVID-19 and AKI, with the occurrence ranging from 0.5% to 46%, depending on the severity of COVID-19.[21]

Alongside respiratory failure and low oxygen levels, COVID-19 often presents as kidney disease. The histopathologic findings emphasize the resemblances between those experiencing AKI in sepsis cases not connected to COVID-19 and those with AKI in COVID-19 patients. Acute tubular injury results in a reduction in renal function. Systemic hemodynamic instability contributes to the development of tubular injury. Despite COVID-19 being labeled as a cytokine storm disease, individuals with non-COVID-19 associated acute respiratory distress syndrome often exhibit lower amounts of circulating cytokines. Endothelial damage and microvascular thrombus formation are two important factors contributing to kidney injury, which are caused by tissue inflammation and infiltration of immune cells. The identification of a significant amount of virus in patients with AKI who are close to death suggests that the invasion of the kidneys by the virus may have had a role.[22]

The study found that the majority of COVID-19 patients who received remdesivir medication and experienced AKI were aged 60 years or older (75%) and had underlying health conditions (84.4%). The analysis employing the chi-square test indicated a statistically significant connection ($p < 0.05$) between the patient's age and comorbidities and the occurrence of AKI. This finding aligns with the research conducted by Wu (2022), which indicates that the incidence of AKI is most prevalent among those aged 65 years or older.[20] In Schaubroeck's study (2022), the findings of a multivariable regression analysis were presented, demonstrating the correlation between age and AKI. The reason for this can be attributed to the fact that patients with AKI tend to be of advanced age, have a higher body mass index, and are more frequently afflicted with diabetes and hypertension compared to individuals without AKI.[23]

Physiological renal function starts to decrease between the ages of 30 and 40 due to the reaction of the renal vasculature to mediators such as acetylcholine and angiotensin. Glomerulosclerosis often appears as fibrosis within the glomerular capsule, thickening of the glomerulus, and collapse of the blood vessels. The process of aging also leads to the formation of tubular atrophy and interstitial fibrosis, characterized by the accumulation of collagen. Additionally, as individuals grow older, they are more susceptible to the development of arteriosclerosis, medial hypertrophy, and hyalinosis of the arterioles. These conditions can result in ischemia, nephron degeneration, and glomerular disease.[24]

Several variables increase the likelihood of developing AKI in individuals who are 65 years of age or older. Comorbidities such as diabetes mellitus, heart failure, and hypertension can cause damage to the renal vasculature. The use of medications such as angiotensin receptor blockers or angiotensin-converting enzyme inhibitors is often associated with comorbidities that can increase the risk of AKI. Nephrotoxic substances, such as nonsteroidal anti-inflammatory drugs and contrast agents containing iodine, are more commonly utilized in older individuals and are recognized to elevate the likelihood of acute kidney injury in patients. Due to their compromised immune systems, the elderly are particularly prone to sepsis, which also increases their susceptibility to developing AKI.[24]

Among COVID-19 patients treated with remdesivir, it was shown that male patients had a much greater occurrence of AKI, with a prevalence of 65.6%. The chi-square test analysis indicated that there was no statistically significant association between the gender variable and the occurrence of AKI. These findings align with Hidayat's (2020) research, which indicates that the chi-square test results show no statistically significant disparity in gender between patients with AKI and those without AKI.[25]

The findings of this study indicate that the mortality rate among COVID-19 patients with AKI who were treated with remdesivir was 53.1%, which is higher than the survival rate. According to Wu's (2022) study, individuals with AKI had a mortality rate of 36.5%. The administration of remdesivir therapy is limited to

patients who are hospitalized with COVID-19 of intermediate severity, which contributes to a poorer prognosis for these individuals. Furthermore, individuals with COVID-19 who experience AKI generally have a more critical medical state compared to people who do not have any kidney impairment.[20]

According to the KDIGO criteria, this study found that 50% of AKI patients had stage 1 AKI. These findings align with Silver's (2021) research, which indicates that stage 1 AKI is the most common, representing 44% of all cases. Stage 3 ranks second with a percentage of 34%, while stage 2 follows with a percentage of 19%.[26]

Out of the 32 patients with AKI included in this study, only 5 patients (15.6%) had RRT in the form of hemodialysis. There is a lack of patients receiving continuous renal replacement therapy (CRRT) methods. Patients receiving RRT have stage 3 AKI. According to a comprehensive study of 154 trials, about 10% of COVID-19 patients who showed AKI had undergone RRT.[26] In Hirsch's (2020) research, 285 COVID-19 patients with AKI requiring RRT were treated using therapeutic methods including intermittent hemodialysis (54%), CRRT (24.6%), and a combination of both therapies (21.4%).[27] KDIGO provides two suggestions about the timing of RRT administration. Immediately, in the case of critical changes in fluid, electrolyte, or acid-base equilibrium, RRT can be promptly commenced. The second guideline is to adopt a comprehensive clinical approach when determining the need for RRT, taking into account various illnesses that can potentially benefit from its administration.[17] These findings align with the results of the study, which showed that 5 patients with AKI who underwent RRT followed the recommendations set by KDIGO guidelines.

Conclusion

The incidence of AKI in COVID-19 patients on remdesivir therapy at Awal Bros Panam Hospital was 13.4%. The older group, namely 65.6% of them, were the primary risk factors for AKI. Additionally, this group had comorbidities in 84.4% of cases. Greater emphasis should be placed on administering remdesivir to COVID-19 patients who are elderly and have comorbidities, as they are at a higher risk of developing AKI.

Limitations of the Study

The limitation of this study is that the majority of patients did not have initial creatinine values; hence, the diagnosis of AKI was only based on the rise in creatinine levels upon hospital admission and the subsequent period of waiting until remdesivir was given. Furthermore, the absence of a control group in this research precluded the examination of the relationship between the incidence of AKI and the administration of remdesivir treatment in patients with COVID-19.

Declarations

Ethics approval and consent to participate

This study was authorized by Awal Bros Panam Hospital's Research Ethics Committee No. 011/RSAB-PNM/KOMED/06.

Competing interests

The authors have no conflicts of interest to declare.

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Author's Contribution

Idea/concept: LPS. Design: ANR, FM. Control/supervision: LPS. Data collection/processing: ANR, FM. Extraction/Analysis/interpretation: ANR, FM, LPS. Literature review: ANR, FM, LPS. Writing the article: ANR, FM, LPS. Critical review: ANR,

FM, LPS. 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

Vitamin D Insufficiency with Elevated ADMA and hs-CRP: A Single-center Study of Chronic Kidney Disease Patients Undergoing Hemodialysis

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ABSTRACT

Background: Vitamin D deficiency is a common issue among patients with chronic kidney disease (CKD) due to its ability to convert vitamin D into the active form of calcitriol, which is crucial for controlling cell inflammation. Low vitamin D levels are associated with increased inflammation and higher levels of biomarkers such as c-reactive protein and asymmetric dimethylarginine as an endogenous inhibitor of nitric oxide synthase. Those two combined become a specific marker for cardiovascular diseases, which become one of the common causes of CKD mortality.
Objective: This study examines the correlation between vitamin D insufficiency, elevated high-sensitivity c-reactive protein, and asymmetric dimethylarginine in CKD patients receiving hemodialysis.
Methods: This study used a cross-sectional design of CKD patients receiving hemodialysis in Dr. Kariadi Central General Hospital, Semarang, Indonesia, in November 2021. Thirty-six patients were randomly enrolled after meeting inclusion and exclusion criteria. Primary outcomes of Vitamin D, hs-CRP, and ADMA were measured from patients' blood after hemodialysis. A statistical analysis of Pearson's correlation was used for primary outcomes.
Results: No significant difference was found in the patient's baseline characteristics. A significant correlation between vitamin D and ADMA has been found; however, no correlation between vitamin D and hs-CRP has been found.
Conclusion: Vitamin D deficiency is correlated with elevated ADMA, indicative of endothelial dysfunction.
Keywords: chronic kidney disease, vitamin D, c-reactive protein, asymmetric dimethylarginine, cardiovascular disease.

Introduction

Chronic kidney disease (CKD) is a growing public health issue.[1] It is estimated that approximately 37 million adults in the United States are affected by this condition. At the same time, Indonesia's prevalence of CKD has continued to rise, with 4 out of 1000 people diagnosed with CKD every year.[2, 3] As a progressive loss of kidney function, CKD often requires long-term and complex medical management, including strict dietary regimens, various medications, and, ultimately, renal replacement therapies like dialysis or transplantation.[4] Cardiovascular disease stands

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out as a leading contributor to increased morbidity and mortality in CKD.[5] This is attributable to the complex interplay between renal impairment and pathological processes such as hypertension, dyslipidemia, and chronic inflammation, which are common in CKD and predispose patients to atherosclerosis and heart failure.[6-8] Additionally, CKD often leads to alterations in mineral metabolism and anemia, further exacerbating cardiac stress.[9, 10]

Vitamin D deficiency is a common and clinically significant issue among patients with CKD.[11] The kidneys play an essential role in converting vitamin D to its active form, calcitriol, which is crucial for controlling the expression of genes that regulate cell inflammation and proliferation.[12] A significant decrease in renal function impairs this conversion process, often leading to vitamin D insufficiency or deficiency in individuals with CKD.[11] Furthermore, Vitamin D is crucial in cardiovascular health, regulating blood pressure, maintaining endothelial function, and preventing arterial stiffness.[13-15] Low vitamin D levels are linked to higher inflammation and elevated biomarkers, such as C-reactive protein, indicating an increased risk for CKD.[16]

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthase, and its accumulation is a well-established marker of cardiovascular risk and endothelial dysfunction in patients with CKD.[17, 18] Elevated levels of ADMA can lead to impaired nitric oxide production, which can result in increased arterial stiffness, endothelial dysfunction, hypertension, and ultimately contribute to cardiovascular diseases.[17] Studies have explored the potential links between these biomarkers and the development of cardiovascular complications in CKD patients, identifying them as potential therapeutic targets to reduce cardiovascular risk.[19, 20]

However, the relationship between vitamin D status, inflammation, and cardiovascular outcomes in CKD patients undergoing hemodialysis remains an ongoing investigation. We hypothesize that vitamin D levels were correlated with systemic inflammatory and endothelial dysfunction, depicted by high-sensitivity C-reactive protein (hs-CRP) and ADMA levels, respectively. This study aims to investigate the correlation between vitamin D insufficiency, elevated hs-CRP as a marker of systemic inflammation, and ADMA as a marker of endothelial dysfunction in a CKD patient receiving hemodialysis at a single-center hospital in Semarang.

Methods

Design and participants

This study employed a cross-sectional design to examine the association between vitamin D status and hs-CRP levels in CKD patients undergoing hemodialysis at Dr. Kariadi Central General Hospital, Semarang, Indonesia, starting in November 2021. The Ethics Committee of Dr. Kariadi Central General Hospital approved this study. The study population consisted of adult CKD patients receiving maintenance hemodialysis at the Nephrology Outpatient Clinic of Dr. Kariadi Central General Hospital during the study period. To be included, patients must be 18 years or older, have a normal body mass index, have been on hemodialysis for at least 3 months, and have provided written informed consent. Exclusion criteria are a history of parathyroidectomy, malignancy, severe liver disease, or if they were taking vitamin D supplements or medications that could significantly impact vitamin D and inflammatory status. A minimum sample of 29 patients was randomly selected to participate in the study.

Outcomes

Primary outcomes

The primary outcomes were serum 25-hydroxyvitamin D (25D) levels and high-sensitivity C-reactive protein (hs-CRP) levels, high-sensitivity C-reactive protein (hs-CRP) and Asymmetric Dimethylarginine (ADMA) levels in the study population. All measurements were conducted using Enzyme-linked immunosorbent assay (ELISA) with blood samples collected from the venous line before the dialysis session.

Vitamin D deficiency was defined as serum 25(OH)D levels <20 ng/mL, insufficiency as 20-30 ng/mL, and sufficiency as >30 ng/mL. High-sensitivity C-reactive protein (hs-CRP) levels >3 mg/L were considered elevated, indicating increased systemic inflammation. ADMA levels >100 ng/mL were considered elevated.

Secondary outcomes

The study also collected baseline clinical and demographic data from the patients, including age, gender, duration of hemodialysis, presence of diabetes, hypertension, and other comorbidities. Hemoglobin was obtained from medical records to assess anemia status.

Statistical analysis

Descriptive statistics were employed to characterize the study population. The relationship between vitamin D status, hs-CRP, and ADMA was assessed using Pearson's correlation coefficient. One-way ANOVA was applied to compare mean hs-CRP levels across different vitamin D status groups. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 24 (IBM Corp.).

Results

The final analysis included a total of 36 CKD patients undergoing hemodialysis. These patients were all enrolled at the Nephrology Outpatient Clinic of Dr. Kariadi Central General Hospital. Of all the patients, the majority were male (55%), and the mean age was 49.11 + 11.86 years old. The average duration of hemodialysis was 21.17 + 17.84 months. Most of the patients have hypertension as a comorbidity (97%). The homogeneity test showed no significant difference (P>0.05) in the clinical characteristics (Table 1).

Table 1. Characteristics of samples from chronic kidney disease patients undergoing hemodialysis in Dr. Kariadi Central General Hospital, Semarang, Indonesia

Characteristics	n (%)	P
Sex		
Male	20 (55)	0.254
Female	16(45)	
Diabetes Mellitus		
Yes	7 (19)	0.161
No	29 (81)	
Hypertension		
Yes	35 (97)	0.167
No	1 (3)	
Use of Angiotensin drugs (ACE-I or ARB)		
Yes	33 (91)	
No	3 (9)	0.079
	Mean	
Age	49.11 ± 11.86	0.225
Haemoglobin	9.08 ± 1.06	0.586
Duration of Haemodialysis (month)	21.17 ± 17.84	0.317
Vitamin D	19.64 ± 8.04	0.704
hs-CRP	14.38 ± 26.55	0.613
BMI	23.54 ± 2.94	0.623
ADMA	105.44 ± 17.48	0.635

The mean serum 25-hydroxyvitamin D level was 20.66 + 11. ng/mL, with 22 patients (61%) having vitamin D deficiency (<20 ng/mL), 9 patients (25%) having vitamin D insufficiency, and 5 patients (14%) having sufficient vitamin D levels. The mean hs-CRP level was 14.38 + 26.55

mg/L, with 23 patients (64%) having elevated levels. The mean ADMA level was 105.44 + 17.48 ng/mL, with 24 patients (67%) having elevated levels.

Pearson's correlation analysis showed a significant negative correlation between serum 25-hydroxyvitamin D levels and ADMA (r = -0.359, p = 0.032). However, there was no significant correlation between 25(OH)D and hs-CRP levels (r = -0.202, p = 0.236), even though a negative correlation trend was shown on the scatter plot (Figure 1). A significant correlation has been shown in ADMA levels, however no correlation found in hs-CRP levels.

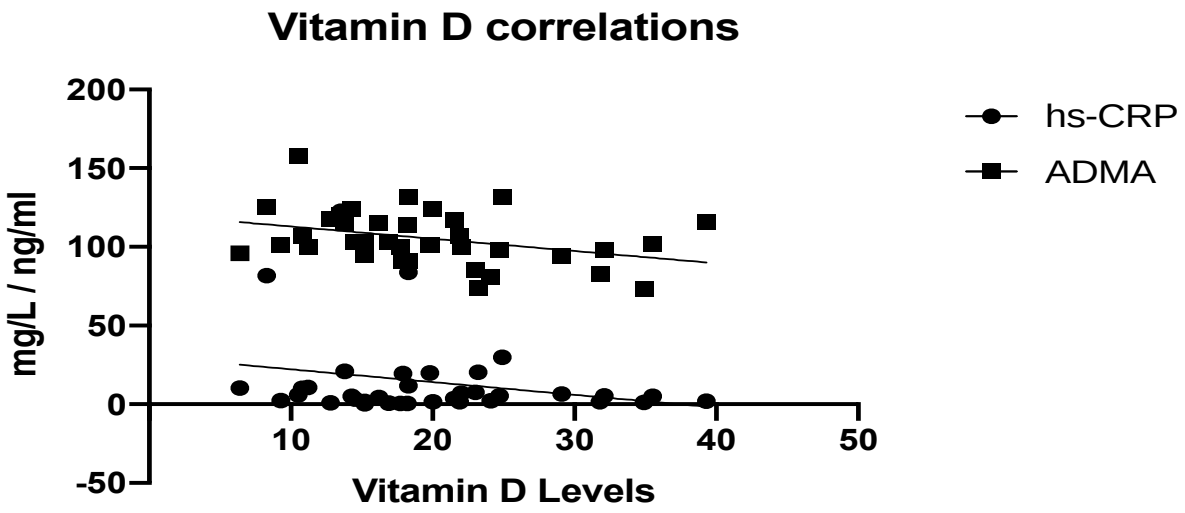

Figure 1. The correlations between vitamin D levels and hs-CRP and ADMA

One-way ANOVA analysis revealed no significant difference in mean hs-CRP levels among the different vitamin D status groups (P=0.497).

Analysis of clinical characteristics indicated that patients with diabetes and hypertension did not have significantly higher mean ADMA levels than those without these comorbidities (P=0.097 and 0.587, respectively), meaning that comorbidities were not involved in the ADMA levels. Hemoglobin levels were also not correlated with ADMA levels (P=0.426) (Figure 2).

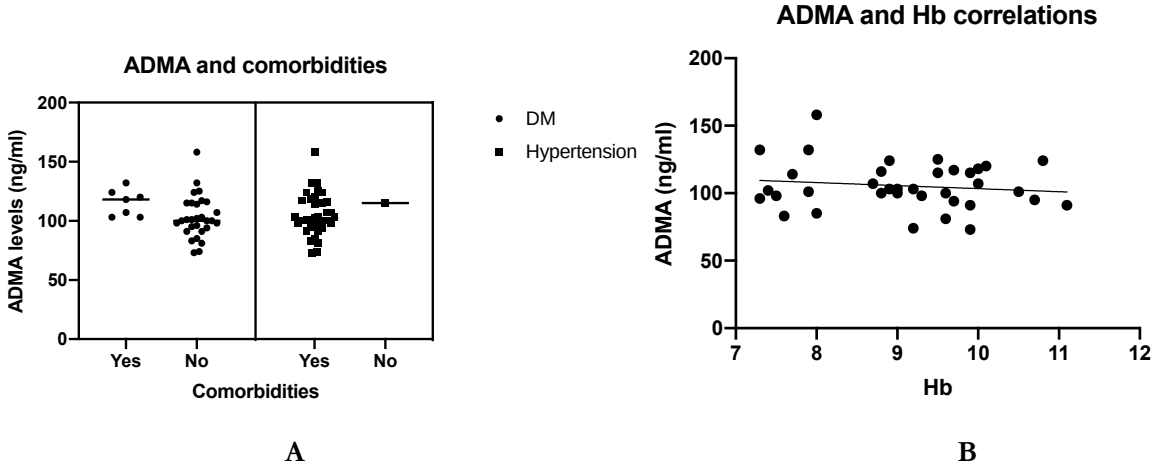

Figure 2. Correlations between confounding factors that may affect ADMA levels

2A shows correlations between ADMA and confounding factors that mostly impact endothelial dysfunction. No significant correlation was found between those two factors with ADMA levels. Figure 2B shows no correlation between ADMA levels and hemoglobin, which may also interfere with endothelial dysfunction.

Discussion

Vitamin D insufficiency is a prevalent complication in CKD patients due to their kidneys' ability to convert vitamin D into calcitriol, its active form.[12] However, in CKD, diminished kidney function hinders this process, often leading to insufficient levels of active vitamin D.[19] Vitamin D also possesses anti-inflammatory properties and contributes to maintaining endothelial function and regulating blood pressure.[16] Thus, in CKD patients, vitamin D deficiency poses a threat to elevate the risk of cardiovascular complications, which already constitute a leading cause of mortality in this patient group.

To counter these issues, CKD management often involves monitoring vitamin D levels, dietary modifications, and possibly supplementation to maintain sufficient vitamin D status and mitigate its associated risks.[11] Recognizing the multifaceted implications of vitamin D deficiency in CKD is vital, extending beyond bone health to cardiovascular risk and overall quality of life.[4]

Vitamin D deficiency in CKD patients can significantly impact inflammation levels, as hs-CRP measurements indicate.[21] Vitamin D is thought to possess anti-inflammatory properties; therefore, insufficient levels may fail to exert a normal regulatory influence on the immune system, potentially resulting in an increased inflammatory response.[22] When vitamin D levels are low, pro-inflammatory cytokines and other inflammatory mediators may be upregulated in the body.[23] This inflammatory state is measurable by hs-CRP, a sensitive marker of systemic inflammation and a predictor of cardiovascular disease risk.[24-26] Elevated levels of hs-CRP have been associated with a higher risk of cardiovascular events, particularly in CKD patients, who are already at heightened risk for cardiovascular disease.

The impact of the interplay between vitamin D deficiency and elevated hs-CRP is thus two-fold. Firstly, it may accelerate the progression of cardiovascular complications, which are a significant cause of morbidity and mortality in CKD patients.[27] Secondly, persistent inflammation can further damage kidney tissue, exacerbating the decline in renal function and potentially accelerating the progression toward end-stage renal disease.[28] While ADMA has been established as a marker of endothelial dysfunction and a predictor of cardiovascular risk in CKD, the specific relationship between vitamin D status and ADMA levels remains less clear.[17, 18]

Our first outcome shows no significant correlation between vitamin D status and hs-CRP levels in our study of CKD patients. However, we may see a suggesting trend that as vitamin D levels increase, hs-CRP levels tend to decrease, though the relationship is not statistically significant. This might be attributed to the relatively small sample size and the complex interplay of various factors affecting the vitamin D-inflammation relationship in CKD. Further research is necessary to explore the nuances of this association and the potential therapeutic implications of vitamin D supplementation for mitigating inflammation in CKD patients.[23]

Another primary outcome highlights the inverse correlation between CKD patients' vitamin D status and ADMA levels. This also aligns with previous studies that revealed a similar inverse relationship between vitamin D and ADMA in various populations.[29] However, the secondary outcome showed no correlations between comorbidities factors and ADMA levels, even though the scatterplot showed that hypertension may affect ADMA levels. An analysis of systole levels and ADMA levels may be helpful to explain the correlation. This result highlighted that the increase in ADMA is strongly

suggested to come from lower Vitamin D levels and neglected all confounding factors.

One potential mechanism by which vitamin D may exert a protective effect on endothelial function is its ability to modulate NO synthesis.[30] Vitamin D has been shown to upregulate the expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing nitric oxide. This critical vasodilator helps maintain vascular tone and endothelial integrity.[31, 32] Vitamin D has been demonstrated to possess anti-inflammatory properties, and its deficiency has been associated with increased oxidative stress and vascular inflammation.[33] These factors can contribute to the accumulation of ADMA, an endogenous inhibitor of nitric oxide synthase, ultimately impairing endothelial function and promoting the development of cardiovascular diseases.[34]

Conclusion

In conclusion, our findings suggest that vitamin D deficiency is associated with elevated ADMA, indicative of endothelial dysfunction, in CKD patients on maintenance hemodialysis. This has implications for the management of CKD, as addressing vitamin D deficiency may be a potential approach to mitigate inflammation-related cardiovascular risks in this high-risk patient population. However, further research is necessary to better understand the complex interplay between vitamin D, inflammation, and cardiovascular outcomes in CKD.

Limitations of the Study

The limitations of this study include its relatively small sample size and cross-sectional design, which preclude any inference of causality. This warrants larger, longitudinal investigations to better characterize the relationships between vitamin D status, inflammation, endothelial function, and other metabolic parameters in the CKD population. Furthermore, an analysis of confounding factors that may alter vitamin D levels externally is needed, such as direct sun exposure, skin type and disorder, and vitamin D absorption disturbance.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Dr. Kariadi Central General Hospital approved this study and the participants have provided written informed consent.

Competing interests

There are no conflicts of interest in writing this article. This article is written neutrally with actual results.

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Author's Contribution

Idea/concept: LL. Design: LL, DLP, SC, AA, AN. Control/supervision: LL, DLP, SC, AA, AN. Data collection/processing: LL, DLP, SC, AA, AN. Analysis/interpretation: LL, DLP, SC, AA, AN. Literature review: LL, DLP, SC, AA, AN. Writing the article: FRM. Critical review: LL. 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

Estimated Glomerular Filtration Rate and Sleep Quality in Stage 3-5 Non-Dialysis Chronic Kidney Disease Patients: Is There a Correlation?

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ABSTRACT

Background: Chronic kidney disease (CKD) is a growing health issue that significantly affects patients' quality of life. CKD patients are prone to sleep disturbances, which can lead to chronic fatigue and a decrease in their quality of life. The Pittsburgh Sleep Quality Index (PSQI) is a parameter that can be used to assess the sleep quality of CKD patients.
Objective: This study aims to determine the relationship between estimated glomerular filtration rate (eGFR) and sleep quality in non-dialysis CKD patients.
Methods: The research design is an observational analytic study with a cross-sectional approach. The research subjects were stage 3-5 non-dialysis CKD patients aged 18 to 60 years at Prof. Dr. R. D. Kandou Hospital Manado from March to May 2022. The sleep quality of CKD patients was assessed using the PSQI score. Data analysis was performed with a significance level of $p < 0.05$.
Results: A total of 30 patients with stage 3-5 non-dialysis CKD were found. They consisted of 20 males and 10 females, aged 38-59 years, with an average of 59.80 ± 9.86 years. In the normality test using Shapiro-Wilk, the patient samples were not normally distributed ($p = .000$). For statistical analysis using the Spearman test, a negative correlation was found between eGFR and PSQI scores ($r = -0.554$), which was statistically significant ($p = 0.002$).
Conclusion: This study found a significant relationship between eGFR and PSQI scores, which shows that a decrease in eGFR worsens the sleep quality of non-dialysis CKD patients.
Keywords: eGFR, PSQI, CKD.

Introduction

Kidney Disease Improving Global Outcomes (KDIGO) defines chronic kidney disease (CKD) as a persistent impairment in kidney structure or function that lasts longer than 3 months. This condition can present as functional or structural abnormalities, with or without a decline in glomerular filtration rate (GFR), and include pathological manifestations indicating kidney abnormalities. These include, regardless of kidney damage, abnormalities in the composition of blood or urine, abnormal imaging tests, and GFR below 60 ml/min/1.73m2 for 3 months.[1] With CKD prevalence increasing to 57% per year, it is becoming a growing health concern. In the United States, the incidence of chronic kidney failure has reached 10% or 1 in 10 people, with a high mortality rate of 615,000 patients experiencing chronic kidney failure, of which 92,000 patients died from chronic kidney failure in 2011.[2]

The incidence of chronic kidney failure in Indonesia is increasing. This disease is described as an iceberg phenomenon, where only about 0.1% of cases are detected, and 11-16% are undetected. Based on statistical data collected by the Indonesian Nephrology Association

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(Pernefri) in 2012, the number of patients with kidney failure increased by 10% from 2011 to 19,621 new patients, with 9,161 patients actively undergoing Hemodialysis therapy.[3]

Poor sleep quality often occurs in CKD patients, especially those who undergo hemodialysis. Daily sleepiness was the most frequently reported symptom, affecting 80% of CKD patients who experienced sleep disturbance at night.[4] This condition leads to negative impacts on hemodynamic changes, thus posing a significant risk for hypertension and complicating the process of hemodialysis. Previous studies have also shown that sleep apnea is linked to a higher risk of heart problems and increased mortality in patients with end-stage renal disease (ESRD).[4] Furthermore, chronic sleep deprivation can affect emotional condition, cognitive function, and memory function.[5-8]

One parameter used to assess an individual's sleep quality is the Pittsburgh Sleep Quality Index (PSQI). It includes 19 items grouped into 7 components, generates a single global score, and takes about 5 to 10 minutes to complete. Researchers at the University of Pittsburgh developed it. Components assessed in the PSQI include total sleep time, amount of time spent asleep, types of disturbances that may cause awakenings during sleep, whether medications influence sleep, and whether there is daytime drowsiness during daily activities.[9]

Poor health-related quality of life remains a challenge for patients with advanced CKD. The purpose of this study is to determine the relationship between glomerular filtration rate (GFR) in non-dialysis CKD patients and sleep quality.

Methods

Design and participants

The research design is an analytical observational study using a cross-sectional approach. The study subjects are non-dialysis CKD patients in stages 3 to 5, aged between 38 and 59, treated at Prof. Dr. R. D. Kandou Teaching Hospital between March and May 2022. The Pittsburgh Sleep Quality Index (PSQI), which consists of 19 items, was used to assess sleep quality. It is a self-administered questionnaire that evaluates patients' sleep quality for the previous 30 days.

Based on the patient's responses, the 19 questions are grouped into seven score components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored from 0 to 3 to generate a global PSQI score ranging from 0 to 21. Higher PSQI scores indicate poor sleep quality, while a PSQI score <5 suggests good sleep quality.

Study covariates

Chronic Kidney Disease

Chronic Kidney Disease (CKD) is a significant health issue worldwide. According to the Kidney Disease Improving Global Outcomes (KDIGO), CKD is defined as an abnormality in kidney function or structure lasting for more than 3 months, characterized by structural or functional abnormalities, with or without a decrease in glomerular filtration rate (GFR) with pathological manifestations, indicating signs of kidney abnormalities, including abnormalities in blood or urine composition, or abnormalities in imaging tests; and GFR less than 60 ml/min/1.73m2 for 3 months, with or without kidney damage.[10] The CKD staging was based eGFR levels (CKD-EPI) using KDIGO classification: eGFR 45-59 ml/min/1.73m^2 was classified as stage 3a, eGFR 30-44 ml/min/1.73m^2 was classified as stage 3b, eGFR 15-29 ml/min/1.73m^2 was classified as stage 4, and eGFR less than 15 ml/min/1.73m^2 was classified as stage 5.[11]

Quality of Sleep

Sleep quality disturbances are a collection of symptoms experienced by patients, including symptoms related to sleep duration, sleep latency, medications needed for sleep, and daytime complaints expressed by the patient.[12]

Pittsburgh Sleep Quality Index (PSQI)

The parameter of sleep quality is a complex phenomenon that consists of quantitative components, such as sleep duration and sleep latency, and qualitative elements that vary between individuals. While sleep quality can be clinically assessed, the subjective components make it challenging to define and objectively measure. Buysse developed the Pittsburgh Sleep Quality Index (PSQI) in 1988, providing a standardized index that clinicians and patients can use to measure sleep quality. The PSQI questionnaire measures sleep quality over a 1-month interval through 19 questions that assess 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction.[9]

Statistical analysis

Data analysis is conducted using SPSS version 27.0.0. A distributive statistic was used to calculate the means and standard deviation of the variables. The Shapiro-Wilk test was used to perform a normality test because the sample size was less than 50. If the data have a normal distribution ($p > 0.05$), the correlation analysis will be done using Pearson's test. Otherwise, Spearman's rank correlation test will be used. A 95% confidence interval was set, and a p-value less than 0.05 was considered significant.

Results

This study identified 30 non-dialysis CKD patients, comprising 20 males and 10 females, with an average age of 59.80 ± 9.86 years. The mean PSQI score was 9.50 ± 5.10 for males and 10.70 ± 4.97 for females. The mean eGFR for males and females was 18.30 ±12.85 and 20.60 ±35.09, respectively.

Table 1. Baseline characteristics of patients included in our study

Variables	Mean ± SD
Age	59.80 ± 9.86
Male	59.95 ± 10.12
Female	59.50 ± 9.86
PSQI	9.90 ± 5.01
Male	9.50 ± 5.10
Female	10.70 ± 4.97
eGFR	19.01 ± 22.17
Male	18.30 ±12.85
Female	20.60 ±35.09

Shapiro-Wilk test showed that the patient samples were not normally distributed (p=.000). As a result, Spearman's rank correlation test revealed a significant negative correlation between eGFR and PSQI score (r=-0.554, p=0.002).

Discussion

The direct effect of insomnia on CKD progression is associated with the dysregulation of blood pressure and the renal-angiotensin-aldosterone system (RAAS). During a normal sleep cycle, which is defined as 90 minutes of alternating between non-rapid eye movement (NREM) and rapid eye movement (REM), there is a slight fall in the blood pressure that triggers plasma renin activity (PRA). Later, this increase in PRA and aldosterone levels is observed in healthy subjects with sufficient night sleep and absent in sleep-deprived subjects. Thus, reduced sleep quality can lead to blood pressure dysregulation and contribute to CKD progression. Restless leg syndrome, characterized by involuntary limb movement, can cause sleep fragmentation and shorten the NREM/REM cycle.[13]

This study found that low eGFR levels are associated with poor sleep quality. This is

consistent with the findings of Tan et al. (2022), who reported that approximately half of CKD patients have poor sleep quality. CKD patients are prone to insomnia due to increased sleep latency, obstructive sleep apnea, restless leg syndrome, and a disturbed sleeping cycle.[14] Decreased production of serotonin and melatonin hormones in individuals over 60 can affect sleep processes and patterns, leading to sleep difficulties. A previous study conducted in Jakarta, Indonesia, in 2019 revealed that more than half of the hemodialysis subjects had experienced insomnia, and the main factors contributing to the sleep disturbance were depression and the duration of hemodialysis.[15] Anxiety in non-dialysis CKD patients is one of the problems affecting their sleep quality. Uremia conditions can disrupt melatonin hormone levels, affecting patient sleep quality.[16]

This finding is also consistent with the previous study by Shafi et al. (2017), which suggests that the sleep quality of dialysis and non-dialysis patients does not differ and indicates the presence of sleep quality disturbances in CKD patients.[17] It was found that there was a U-shaped association between sleep duration and the worsening of CKD. Sleeping less than 5 hours or more than 8 hours contributed to the progression of the renal disease.[7] However, another study conducted by Cao W et al. (2022) showed no direct relationship between decreased eGFR and sleep quality.[13] This contradictory result with the current study could also be possible because the researchers did not include patients over 60 years old, as these physiological processes experienced by geriatric patients are considered normal. Another study by Luca G. (2015) indicated that with increasing age, sleep quality improves.[18]

Conclusion

This study found a significant positive correlation between eGFR and PSQI score, indicating that a decrease in eGFR worsens sleep quality in non-dialysis CKD patients in stages 3-5.

Limitations of the Study

This study has several limitations. Further elaboration on the specific sleep disturbances experienced by patients is needed, which could provide a clearer understanding of the relationship. Therefore, the researchers suggest further research to explain better the association between eGFR and sleep disturbances in CKD patients. These varying research results indicate that sleep quality assessments should continue to be conducted to monitor patients' quality of life.

Declarations

Ethics approval and consent to participate

This article complied with all ethical rules at the research site.

Competing interests

The authors have no conflicts of interest to declare.

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Author's Contribution

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

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Review Article

A Review of Central Vein Catheter for Hemodialysis: Insertion Sites and Techniques

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ABSTRACT

Chronic kidney disease (CKD) is a global epidemic, being increasingly prevalent in both developed and developing countries, including Indonesia. Hemodialysis (HD) is the primary renal replacement therapy, along with peritoneal dialysis and kidney transplantation. The effectiveness of HD relies on well-functioning vascular access, such as central vein catheters (CVCs). These catheters are classified by their duration of use: short-term, medium-term, and long-term. They are also distinguished by insertion type (central or peripheral), insertion site (jugular, subclavian, femoral), and number of lumens (single, double, triple). The preferred site for insertion is the internal jugular vein, followed by the femoral vein and the subclavian vein. Techniques for CVC insertion include the central approach, the posterior approach, and others. This article reviews the role of CVC for vascular access in HD. Specifically, various CVC insertion sites and techniques will be examined. The authors will also discuss the available research on the application of CVC as vascular access for HD in Indonesia.

Keywords: Chronic kidney disease, hemodialysis, central venous catheter, techniques, insertion sites.

Introduction

Chronic kidney disease (CKD) has emerged as a worldwide epidemic, with its incidence rising across both developed and developing nations. In Indonesia, CKD affects 12.5% of the adult population. Most CKD patients die from cardiovascular complications. Only a small percentage reach the terminal stage, requiring kidney replacement treatment. It is estimated that 100,000 patients require kidney replacement treatment in Indonesia.[1]

In most countries globally, hemodialysis (HD) remains the primary renal replacement therapy, alongside peritoneal dialysis and kidney transplantation. Over 2 million patients around the world are currently receiving HD treatment. In Indonesia, almost 150,000 people.[1] Effective HD requires adequately functioning vascular access. The optimal access should permit the use of two needles, enable a 300 ml/minute blood flow rate, be resistant to thrombosis and infection, and have minimal side effects.[2-4] This access may be an arteriovenous fistula (AVF), a graft, or a central venous catheter (CVC).[1]

AVF is preferred for HD vascular access due to the higher incidence of complications such as infection and thrombosis associated with grafts and CVC.[5] However, it takes at least 6 weeks for the AVF to be usable, and sometimes additional surgical intervention is required for the AVF to mature and be usable.[6, 7] For those with heart failure, chronic lung disease, or steal syndrome, AVF may not be the best option since it can result in intense pain and peripheral ischemia. On the other hand, grafts can be used for cannulation approximately 2-3 weeks after

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being implanted. However, grafts are generally not the preferred option for vascular access in hemodialysis patients.[8, 9] Therefore, CVC, whether temporary or permanent CVC, can be considered as vascular access for HD patients with such conditions.

This article reviews the role of CVC as a vascular access in HD. Specifically, various CVC insertion sites and techniques will be examined. The authors will also discuss the available research on the application of CVC as vascular access for HD in Indonesia.

Central Vein Catheter (CVC)

CVC insertion is a frequently performed procedure carried out in approximately 8% of hospitalized patients. It is also indicated in various treatments, such as plasmapheresis, HD, placement of defibrillator devices, and other procedures. The patient's anatomy and the indications for the CVC insertion, among other factors, determine the insertion sites and the number of lumens on the catheter.[10, 11]

The CVC is an appropriate option for vascular access when urgent or emergent HD is needed, such as in acute conditions or when other accesses are unfit. Due to its multiple insertion sites, the CVC is highly accessible and flexible. Furthermore, it provides swift access for HD as no maturation is necessary.[12] CVCs are typically categorized by 1) duration of use: short-term, medium-term, and long-term; 2) insertion method: central or peripheral; 3) insertion site: jugular, subclavian, femoral, and brachial; and 4) a number of lumens: single-lumen and multi-lumen.[13]

Catheters for HD usually have 2 lumens attached to 2 portals, one red and the other blue. The red portal indicates that the lumen is connected to the artery; hence, it draws blood from the body. Meanwhile, the blue portal suggests that the lumen is connected to the vein; thus, it returns blood from the HD machine back to the patient's body.[14]

Compared to catheters used for CVC in general, those used for HD have a larger diameter to produce greater flow velocity. This is in accordance with Poiseuille's law, which posits that a catheter's flow rate is influenced by its resistance to flow and is directly proportional to the length of the catheter and inversely proportional to its diameter. It is also affected by viscosity, which causes a higher resistance.[14]

Landmark and Methods of CVC Insertion

The choice of where to place a central vein catheter depends on several factors: the operator's proficiency, the patient's anatomy (such as existing venous blockages or lymphedema), potential risks like clotting issues or pulmonary disease, and specific needs related to the condition of patient and the length of time the catheter will be needed.[15-19]

The ideal insertion site should be clean and free from contamination. Contaminated areas include areas in proximity to tracheostomies or open surgical wounds, and burned or infected skin.[15] Furthermore, catheterization of sites that have experienced local anatomical alterations (such as healed clavicle fractures), scarring from previous accesses, or where there is already a central venous catheter or other implanted devices (like pacemakers or internal defibrillators) increases the likelihood of complications including failure, misplacement, dysrhythmias, and other issues. Whenever possible, alternative sites should be considered to minimize these risks.[6, 17] The presence of substantial lung disease affecting one side should warrant inserting the CVC on the contralateral side.[13]

The internal jugular vein, femoral vein, and subclavian vein are commonly selected sites for placing a CVC. Ultrasonography plays a crucial role in this process. It facilitates prompt and precise identification of the veins while also yielding information such as venous pressure and thrombus presence.[20] The benefits and drawbacks of each site are elaborated in Table 1.[13]

Table 1. Advantages and disadvantages of venous access based on insertion location.

Approach	Advantages	Disadvantages
External jugular	• Superficial vessel that is often visible • Coagulopathy not prohibitive • Minimal risk of pneumothorax (especially with US guidance) • Head-of-table access • Prominent in older adult patients • Rapid venous access	• Not ideal for prolonged venous access • Poor landmarks in patients with obesity • High rate of malposition • Catheter may be difficult to thread
Internal jugular	• Minimal risk of pneumothorax (especially with US guidance) • Head-of-table access • Procedure-related bleeding amenable to direct pressure • Lower failure rate with novice operator • Excellent target using US guidance	• Not ideal for prolonged access • Risk of carotid artery puncture • Uncomfortable • Dressings and catheter difficult to maintain • Thoracic duct injury possible on left • Poor landmarks in patients with obesity/edematous patients • Potential access and maintenance issues with concomitant tracheostomy • Vein prone to collapse with hypovolemia • Difficult access during emergencies when airway control being established
Subclavian	• Easier to maintain dressings • More comfortable for patient • Better landmarks in patients with obesity • Accessible when airway control is being established • Associated with lower incidence of catheter-related infection*[1]	• Increased risk of pneumothorax • Procedure-related bleeding less amenable to direct pressure • Decreased success rate with inexperience • Longer path from skin to vessel • Catheter malposition more common (especially right SCV) • Interference with chest compressions • Risk for stenosis/occlusion, which impacts future hemodialysis arteriovenous access
Femoral	• Rapid access with high success rate • Does not interfere with CPR • Does not interfere with intubation • No risk of pneumothorax • Trendelenburg position not necessary during insertion	• Delayed circulation of drugs during CPR • Prevents patient mobilization • Difficult to keep site sterile • Difficult for PA catheter insertion • Increased risk of iliofemoral thrombosis

US: ultrasound; SCV: subclavian vein; CPR: cardiopulmonary resuscitation; PA: pulmonary artery.
*From Parienti, infection rates: subclavian 0.5%; jugular 1.4%; femoral 1.2%.

Internal Jugular Vein

The internal jugular vein extends from the sigmoid sinus as it exits the jugular foramen at the base of the skull. Positioned within the carotid sheath alongside the carotid artery and vagal nerve (Figure 1), these veins typically show asymmetry in size between the left and right sides in patients, with a notable diameter disparity in over one-third of cases. The internal jugular vein's diameter tends to as it progresses downward into the chest.[21-23]

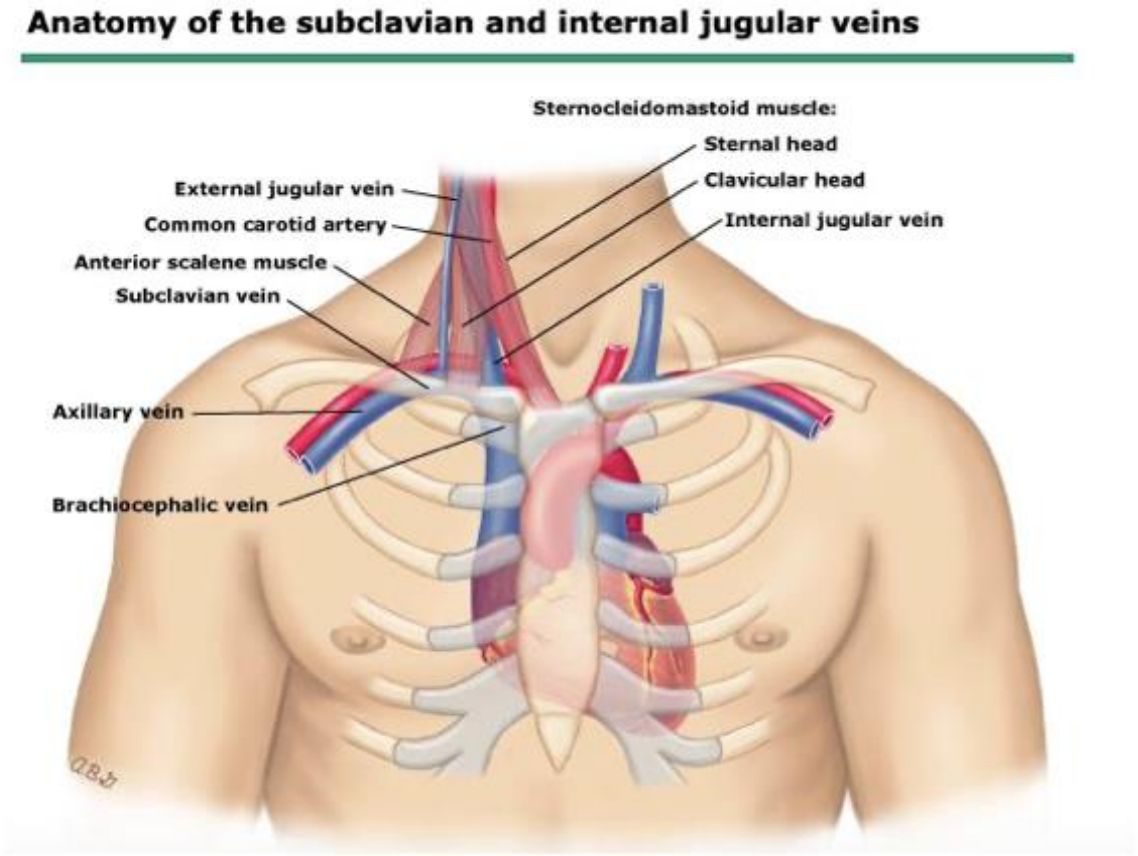

Figure 1. Anatomy of the internal jugular vein and subclavian vein[13]

The internal jugular vein exits the skull towards the internal carotid artery. As it reaches the level of the cricoid cartilage, it runs beneath the sternocleidomastoid muscle, and further down, it lies between the two heads of this muscle at the neck's base. Around this area, the veins are positioned superficially, between 1 and 1.5 cm beneath the skin surface. Eventually, behind the medial end of the clavicle, the internal jugular vein merges with the subclavian vein to form the brachiocephalic vein.[24]

The external jugular vein is a visible superficial neck vein (Figure 2) that runs across the sternocleidomastoid muscle. It connects with the anterior subclavian vein or can be situated just outside the anterior scalene muscle. Typically, the external jugular vein has a diameter exceeding 10 mm, and its size inversely correlates with that of the internal jugular vein.[25]

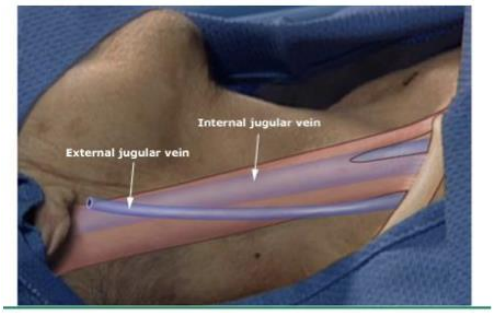

Figure 2. Anatomy of internal jugular vein and external jugular vein[13]

For several reasons, the preferred site for CVC insertion is the internal jugular vein (Figure 3). First, it is a prominent superficial vein that can be readily visualized using ultrasound. Second, this vein provides a direct pathway to the right atrium or superior vena cava, ensuring rapid blood flow. Third, its lower section lies behind a triangular area formed by the junction of the sternomastoid and clavicle muscles, which serves as a landmark for CVC placement.[12] The right internal jugular vein is favored due to lower

malposition risks. However, the left side internal jugular vein may be chosen when extensive scarring or venous thrombosis is present on the right side.[13]

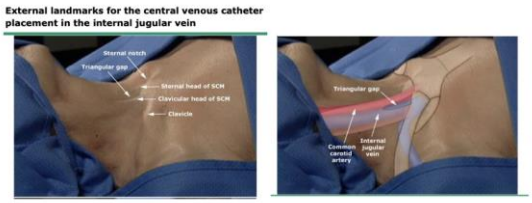

Figure 3. Landmark of CVC insertion through the internal jugular vein[13]

Normally, this vein is located anterolateral to the internal jugular artery, but in some cases, it is located anterior or even medial to the artery.[26] For this reason, ultrasonography is very useful in such cases.[27]

Proper patient positioning involves tilting the head about 10 degrees to insert a CVC. This helps locate the vein effectively and lowers the risk of air embolism.[28] To ensure safety during the procedure, it is advisable to keep the patient's head in a neutral position. As this vein runs closely above the carotid artery, there is a significant risk of accidental puncture into the artery. Minimal rotation of the patient's head towards the side where cannulation is being performed may be required. However, excessive rotation should be avoided since it can compress the vein, potentially reducing its diameter.[29] Moreover, head rotation can cause the vein to shift sideways, further complicating locating it.[30]

Two methods are distinguished by whether the needle is visible during vein entry. One involves using ultrasound, positioning the probe along the long or short axes. Currently, the short axis view from the side has proven effective, making it the preferred method for cannulating the internal jugular vein.[31] The alternative method is direct insertion, also known as the Seldinger technique. This method involves using a guide wire alongside the needle. After the vein is accessed, a guide wire is carefully inserted, and the needle is withdrawn. It's crucial to avoid advancing the wire excessively to prevent irritation of the right atrium and potential arrhythmias. Subsequently, before introducing the catheter, the dilator must be cautiously passed over the guide wire to minimize venous trauma.[32] The Seldinger technique has three approaches: the central approach, the posterior approach, and the anterior approach.[13]

Central Approach

The most utilized method is a central approach to the internal jugular vein (Figure 4). The needle insertion site is identified at the triangular apex created by the sternocleidomastoid muscle, located approximately 5 cm above the clavicle.[13] Table 2 details the steps in performing the central approach for internal jugular vein catheterization.

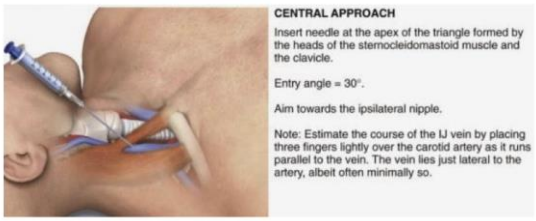

Figure 4. Central approach[13]

Table 2. Steps in performing the central approach technique

1. Insert the needle adjacent to the carotid pulse at a relative 30 to 45-degree angle to the skin.
2. Guide the needle laterally in the sagittal plane toward the nipple on the same side. This path typically runs along or beneath the lateral edge of the sternocleidomastoid muscle.
3. Approaching the jugular vein from medial to lateral may lower the risk of pneumothorax and accidental puncture of the carotid artery.
4. If blood cannot be aspirated within 2.5 cm of depth, slowly withdraw the needle while maintaining continuous negative pressure and check for blood aspiration.
5. If the initial needle insertion is unsuccessful, promptly withdraw the needle to the skin surface and redirect it 10 degrees medially.

Posterior Approach

Table 3 details the steps in performing the posterior approach for internal jugular vein catheterization. To enhance the visibility of the insertion site and potentially improve the success rate of access using the posterior approach (Figure 5), one should turn the head towards the opposite side.[13]

Table 3. Steps in performing the posterior approach technique

1. Place the needle along the back edge of the sternocleidomastoid muscle where its middle and lower sections meet. This spot lies about 5 cm above the clavicle and is typically identifiable by the presence of the external jugular vein.
2. Begin inserting the needle beneath the posterior sternocleidomastoid muscle and proceed in an anteromedial direction toward the sternal notch.
3. Any further adjustment in needle direction should be carried out in a methodical manner, progressing from the outer to the inner needle position

Anterior Approach

Table 4 details the steps in performing the anterior approach for internal jugular vein catheterization. Using the anterior technique, one approaches the internal jugular vein from the point where it enters anterior to the sternal head of the sternocleidomastoid muscle (Figure 6).[13]

Table 4. Steps in performing the anterior approach technique

1. Feel the carotid artery.
2. Place the needle 5 cm above the sternum, precisely at the midpoint of the front edge of the sternocleidomastoid muscle.
3. Guide the needle outward toward the carotid pulse along a trajectory aimed towards the same side's nipple.

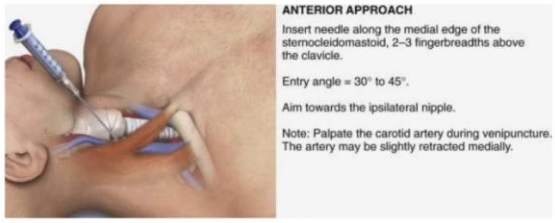

Figure 6. Anterior approach[13]

A catheter inserted through the right jugular vein typically measures approximately 15 cm, while insertion through the left internal jugular vein measures about 17 cm. In the case of a temporary CVC, it is crucial that the tip is positioned outside the right atrium, a placement that should be confirmed during the procedure using electrocardiography or through a post-procedure chest X-ray prior to commencing hemodialysis. In contrast, for a cuffed tunneled catheter, one end of the CVC must reach the right atrium, while the other end should be positioned 1 cm above and outside the right atrium.[12]

Femoral Vein

The primary deep vein in the lower limbs, the femoral vein (Figure 7) travels through the thigh and then becomes superficial in the femoral triangle. It passes under the inguinal ligament and continues into the pelvis as the external iliac vein. Below the inguinal ligament, at the level where the femoral nerve is situated, lie the hip joint and the psoas muscle.

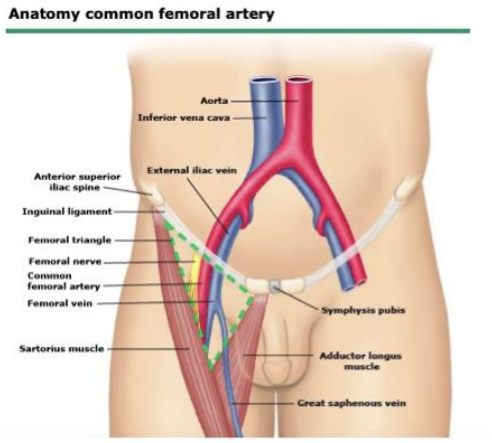

Figure 7. Femoral vein anatomy[13]

In the femoral triangle, the femoral sheath shields the common femoral vein, positioned medially relative to the femoral artery. It receives blood from the anterior saphenous vein and the great saphenous vein. These veins are sometimes mistaken for femoral veins and unintentionally used for cannulation during CVC placement. The femoral artery serves as a landmark to guide needle insertion. The mid-inguinal point lies between the anterior superior iliac spine and the pubic tubercle.

The femoral vein is an alternative site for placing a temporary CVC in hospitalized patients, often chosen when there's a reduced risk of bleeding and no need for immediate post-placement radiological confirmation. Nonetheless, an X-ray verification may be beneficial to ensure proper CVC position. Confirmatory x-ray should show no twisting of the tube and that its tip has not entered unintended veins like the lumbar vein or its branches.[12]

For insertion at the femoral vein, the patient lies on their back with the thigh moved outward and rotated externally. The entry point for the needle into the femoral vein is positioned just under the inguinal ligament (around 2 cm below) and towards the inside of the femoral artery (Figure 8). The needle typically goes about 2–4 cm deep and is inserted at an angle of 10–15°. The femoral vein can also be accessed using the Seldinger technique.[12]

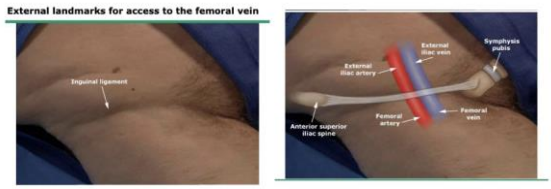

Figure 8. Landmark for CVC insertion via femoral vein[13]

The Valsalva maneuver widens the femoral vein's diameter. Ideally, when inserting the distal tip of a CVC via the iliac vein, it should be positioned optimally in the right atrium or the inferior vena cava. However, typical catheters (20 cm long) frequently only access the iliac vein, resulting in heightened blood recirculation at this tip location. It is important to note that using a longer catheter would increase resistance to blood flow even more.[12]

Subclavian Vein

For subclavian cannulation, the clavicle is the primary reference point (Figure 9). The sternal head appears elongated in an S-shape (double curve horizontally) when moving outward from the suprasternal notch: the middle two-thirds forms the convex anterior portion, while the outer third forms the concave anterior portion.[13]

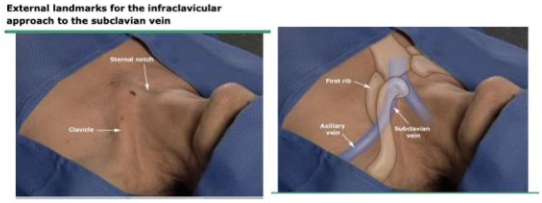

Figure 9. Landmarks for CVC insertion via subclavian vein[13]

The subclavian vein originates as a direct extension of the axillary vein, commencing at the outer edge of the first rib. It arches posteriorly behind the medial clavicle and descends towards the internal jugular vein, which merges to form the brachiocephalic vein behind the sternoclavicular joint. Alongside the subclavian vein runs the subclavian artery, positioned superiorly and posteriorly to the vein, with the anterior scalene muscle separating the two.[13]

Inserting a catheter into the subclavian vein is seen as a less preferred option due to the significant risk of developing subclavian thrombosis. This procedure aims to puncture the upper part of the subclavian vein where it meets the internal jugular vein. Accurately identifying the clavisternomastoid angle, formed by the junction of the lateral aspect of the sternocleidomastoid muscle and the clavicle, is crucial for successful access. Elevating the patient's head actively can enhance visibility of this landmark.

The Seldinger technique allows access through the subclavian vein. It can be performed using three methods: below the collarbone (infraclavicular), above the collarbone

(supraclavicular), and through the armpit (axillary).[13]

Infraclavicular Approach

The infraclavicular approach to the subclavian vein necessitates three insertion points (Figure 10). The midpoint technique is frequently employed in this procedure, wherein the needle is positioned approximately 2 to 3 cm below the midpoint of the clavicle (around 1 to 2 cm lateral to the clavicle's curve) and aimed just behind the suprasternal notch.[33]

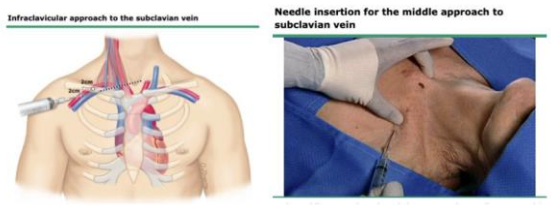

Figure 10. Infraclavicular approach[14]

The lateral needle insertion (outside the midclavicular line) leverages the thinner front section of the clavicle, making it easier to approach at the coronal level. This can enhance safety if the needle can access the vein. The medial insertion point lies along the inner third of the clavicle. To access the larger vein, the needle is directed towards the suprasternal notch. However, this method has a drawback: the steep angle required under the thick medial clavicle and through soft tissues like the costoclavicular ligament.

The needle may initially encounter the clavicle and could puncture the periosteum after breaking through the skin, potentially causing bone fragments to block the needle. To reach the lower edge of the clavicle, the needle should be gently advanced deeper. Throughout this process, it is crucial to keep the needle parallel to the clavicle (in the coronal plane) to pass beneath the bone and reduce the risk of puncturing the pleura. Once the needle reaches below the junction of the middle and medial thirds of the clavicle, it should enter the vein. Adjust by aiming the needle slightly upward during the subsequent insertion if the first attempt is unsuccessful.[33]

Supraclavicular approach

The supraclavicular approach targets puncturing the subclavian vein close to its confluence with the internal jugular vein. The sternocleidomastoid clavicular head region is the landmark for insertion in this technique. The subclavian vein lies at a depth of approximately 1 to 1.5 cm beneath the skin surface and is readily accessible with a needle. To access it, the needle is inserted 1 cm to the side of the outer edge of the sternocleidomastoid muscle and 1 cm behind the clavicle. It should be angled 45° relative to both the front-to-back and side-to-side planes, and at a 15° downward angle from the top-to-bottom plane, aiming towards the opposite nipple (Figure 11).[33] The needle enters an avascular plane by bisecting the angle formed by the clavicle, sternum, and mastoid process. It avoids the subclavian artery and the pleural dome, targeting the confluence of the subclavian vein and internal jugular vein. The right side is favored due to the lower position of the pleural dome, a more direct path to the superior vena cava, and the absence of the thoracic duct.[12]

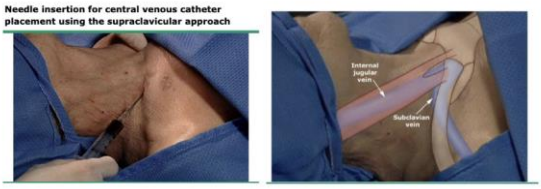

Figure 11. Supraclavicular approach[13]

Axillary approach

The axillary approach is rarely employed. It involves using ultrasonography to locate and access the vein where the subclavian vein meets the axillary vein. The Trendelenburg position is advised to reduce the chances of air embolism and may aid in venous dilation since the subclavian vein lacks superior fascial constraint. To mitigate complications, the needle should point downwards during insertion, and it is crucial to accurately identify the clavisternomastoid angle beforehand. However, this method is associated with increased risks of bleeding, pneumothorax, and thrombosis.[12]

Vascular Access Recommendation

According to KDOQI guidelines, selecting the appropriate location and type of long-term access significantly impacts survival rates and reduces complications. Ideally, vascular access should be distal and situated in the upper extremities. The preferred choice is an AVF, with AVG as a secondary option before considering CVC. CVCs should only be used as a final option when AVF and AVG are not feasible for the patient. The guidelines also stated that the preferred site for placing a dialysis catheter is the right internal jugular vein. However, other alternatives are the right external jugular vein, as well as both the left internal and external jugular veins, the subclavian vein, and the femoral vein. The subclavian vein is considered only when access through the upper extremities or other thoracic areas is not feasible.

KDOQI has issued several basic principles regarding dialysis catheters (Table 5). The use of ultrasound during dialysis catheter insertion and radiological confirmation of the catheter tip is endorsed by KDOQI.

Table 5. Basic principles of catheter use in dialysis

1. Long-term catheters, including tunneled and port catheters, require the catheter tip to be positioned in the right atrium, confirmed by fluoroscopy to ensure adequate flow.
2. Short-term catheters should be placed in the superior vena cava and confirmed by radiology or fluoroscopy before commencing hemodialysis.
3. Non-cuffed dialysis catheters are suitable only for hospitalized patients and should be used for less than one week.
4. A plan should be established to discontinue or transition from a short-term catheter to a long-term catheter within one week.
5. Long-term or port catheters should not be inserted at the same site as an arteriovenous fistula (AVF).
6. The femoral dialysis catheter should be sufficiently long to ensure adequate blood flow and minimize recirculation, aiming for an expected flow rate of 300 ml/min with a recommended catheter length of 24–31 cm.
7. Currently, no evidence shows the superiority of one catheter design over another. The selection of a dialysis catheter should be based on clinical experience, objectives, and cost considerations.
8. Dialysis port catheters can be used alongside long-term catheters as temporary access while awaiting permanent access solutions.

Application of CVC for HD in Indonesia

A 2021 study involving 151 CKD patients in Dr. Mohammad Hoesin, Palembang, Indonesia, found that the most prevalent HD vascular access was temporary vascular access (61%). Most patients with permanent vascular access had a brachiocephalic fistula (46.3%). Meanwhile, long-term double-lumen catheters were most frequently observed in those with temporary vascular access. The most used site in patients with short-term double-lumen catheters was the femoral vein. On the other hand, internal jugular vein access was seen in most patients with long-term double-lumen catheters.[34] Similarly, a 2019 research study of 150 subjects with stadium 4–5 CKD at Cipto Mangunkusumo National Hospital reported that CVC was more often inserted at the internal jugular vein.[35]

A cohort of 151 Indonesian patients undergoing HD in a period of 13 months had an infection rate of 37%, according to a retrospective cohort study by Widani and Suryandari. They concluded that the lengthy duration of catheterization, femoral insertion, and the presence of diabetes mellitus were risk factors for the incidence of infection in patients with double lumen catheter undergoing HD.[36] Ocsyavina and Patrianef reported a 7.53% incidence of central vein stenosis in 717 patients with CVC undergoing HD. They found that the subclavian insertion site (compared to the internal jugular) and previous multiple ipsilateral catheterization were associated with the incidence of central vein stenosis, with an odds ratio of 148.77 and 63.82, respectively.[35]

Conclusion

Vascular access is typically categorized into two types: permanent, such as AVF, and temporary, which involves inserting a central venous catheter. Central venous catheters are classified by the duration of use (short-term, medium-term, and long-term), insertion type (central or peripheral), insertion location (jugular, subclavian, femoral, and brachial), and number of lumens (single, double, or triple). Effective hemodialysis depends on having reliable vascular access. CVCs can provide rapid HD access and may be suitable for certain patients. Sufficient knowledge of anatomy and proper techniques are required to ensure a successful CVC insertion. Apt selection and maintenance of CVCs are crucial for reducing complications and improving patient outcomes in HD treatment. Addressing CKD's rising incidence requires advancing these vascular access techniques and ensuring their practical application.

Declarations

Competing interests

None declared.

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Author's Contribution

Idea/concept: JPS, AR. Design: JPS, AR. Control/supervision: JPS, AR. Data collection/processing: JPS, AR. Analysis/interpretation: JPS, AR. Literature review: JPS, AR. Writing the article: JPS, AR. Critical review: JPS, AR. 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

Severe Clinical Impact of Multiple Wasp Stings: A Case Report of Acute Kidney Injury

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ABSTRACT

Wasp stings are prevalent in Indonesia and have occasionally resulted in fatalities. Wasp stings can potentially induce a small localized allergic response, systemic reactions, or even life-threatening illnesses. Receiving several stings from wasps can cause systemic inflammation, resulting in acute kidney injury. We present a case of a 51-year-old female who experienced severe renal impairment as a result of repeated wasp stings. Following the stings, the patient promptly obtained medical attention. However, on the second day after the incident, the patient's renal function declined and experienced anuria. The ultrasonography indicates the presence of nephritis. The patient presented with 103 sting wounds, which resulted in local reactions and were accompanied by systemic symptoms. The patient was administered high-dose steroids and underwent five intermittent hemodialysis sessions, which effectively restored their kidney function. Evidence of enhanced renal function was demonstrated through the restoration of normal urine production, elevated glomerular filtration rate, and significant clinical improvements in the patient. This case illustrates the severe impact on the kidney of a generalized wasp sting and the effect of promptly receiving medical treatment following an enormous wasp sting on the patient's prognosis. Initiating dialysis promptly is crucial for rapidly eliminating toxins and thus preserving renal function.

Keywords: acute kidney injury, hemodialysis, wasp sting.

Introduction

Insect bites are often caused by Hymenopterans, which belong to three major families: Apidae (bees), Vespidae (wasps), and Formicidae (ants).[1] Indonesia is home to a wide variety of wasps. Wasps exhibit a high level of aggression when protecting their nests.[2] Contrary to bees, wasps can retract their stingers from their victim's skin and then fly away. Wasps can sting multiple times without limitation.[1]

The incidence of Hymenopteran stings is distributed in several regions of Indonesia. Between 2017 and July 2022, Indonesia has recorded 125 incidences of wasp stings, resulting in 12 deaths. The management of the Handling Program for Diseases Caused by Bites/Stings of Poisonous Animals and Poisonous Plants is still inadequate. The Ministry of Health and National Standard Operating Procedures provide instructions for the management of cases involving bites or stings from venomous animals and plants. The limited supply of antivenom is a contributing factor to the ongoing challenge of managing these patients.[3]

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Case Illustration

A 51-year-old female patient experienced edema anasarca during the previous 48 hours. The woman was transported to the local hospital two hours after getting stung. She had conservative therapy and wound cleansing before being transferred to a general hospital. At the second hospital, the patient first received conservative treatment. However, after careful observation, it was determined that the patient needed hemodialysis. As a result, the patient was then referred to Rasyida Kidney Hospital. During the examination, we discovered a total of 103 sting wounds on the patient's body. Specifically, there were 36 wounds on the left leg, 11 on the right leg, 22 on the right hand, 9 on the left hand, 12 on the chest, 5 on the face, and 8 on the back. These wounds varied in size, ranging from 0.5x0.5 cm to 1x1 cm. Several wounds developed into ulcers, while minor wounds started to heal. The patient exhibited symptoms including dyspnea, facial edema, emesis, cephalalgia, reduced urinary output, and edema anasarca. The patient had no prior medical conditions or preexisting renal problems. All vital indicators were within the normal range except for an elevated respiratory rate.

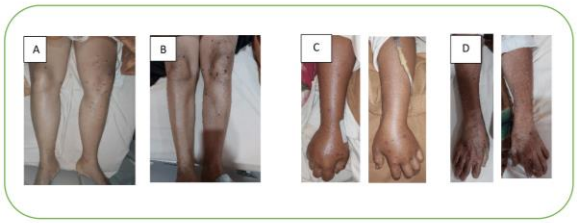

Figure 1. Clinical changes in the patient. A. Both legs on the first day. B. Both legs upon discharge. C. Both hands on the first day. D. Both hands upon discharge.

The laboratory results indicate the following values including hemoglobin: 12.0 g/dL, leukocyte count: 21,400/mm^3, platelet count: 150,000/µL, urea: 155 mg/dL, creatinine: 5.0 mg/dL, estimated Glomerular Filtration Rate (eGFR): 13 mL/min, albumin: 2.0 g/dL, glucose ad random: 115 mg/dL, Sodium: 139 mmol/L, Potassium: 5.26 mmol/L, and Chloride: 111 mmol/L. The arterial blood gas analysis reveals the following values: pH: 7.24, pCO_2: 33.1 mmHg, pO_2: 97.0 mmHg, HCO_3: 14.0 mmol/L, total CO_2: 15.0 mmol/L, base excess: -13.3 mmol/L, and oxygen saturation: 96%. The urinalysis results indicate a pH of 6.5, a significant amount of protein (+++), and the presence of erythrocytes (+). The renal ultrasonography revealed indications of nephritis.

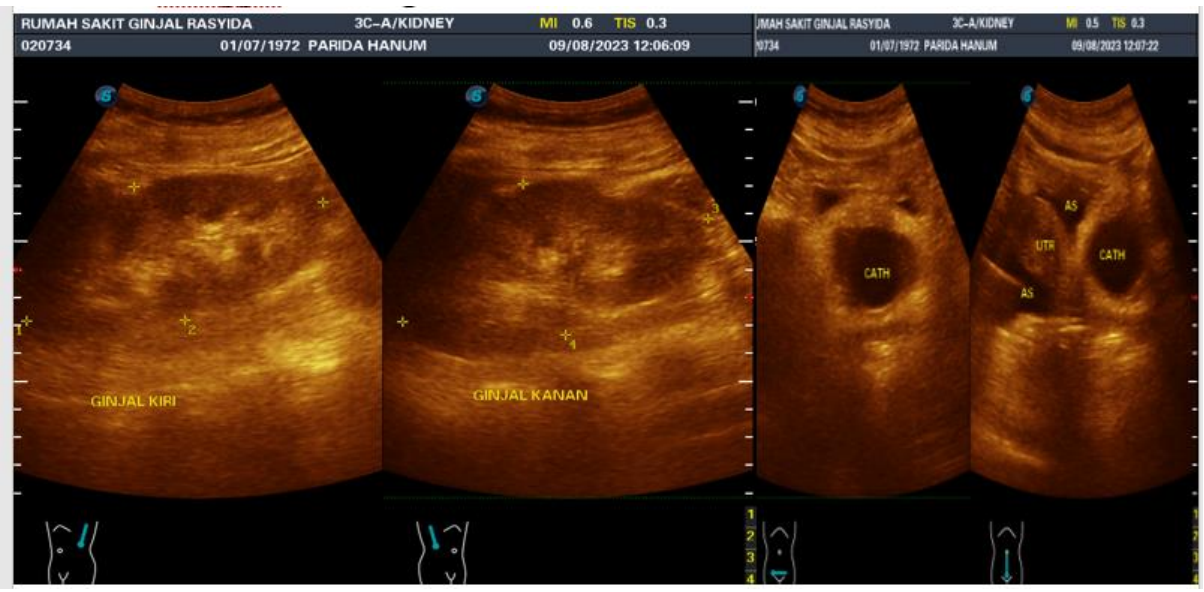

Figure 2. Ultrasonography examination results: showing signs of nephritis.

The patient was administered a large dosage of methylprednisolone intravenously and followed by oral dosages during her outpatient treatment. On the twelfth day of treatment, the patient experienced acute upper gastrointestinal bleeding, even though she had been receiving

proton pump inhibitor therapy since the first day she was admitted. During the following three days, the patient was treated with PPI therapy until the symptoms of upper gastrointestinal bleeding resolved. In addition, the patient presented with oral candidiasis infection, which was characterized by dysphagia and the presence of oral thrush. The edema anasarca was gone entirely on the final day of the treatment. The patient was discharged from the hospital after confirming the absence of digestive problems and an improvement in appetite.

Discussion

The venom of Hymenoptera contains several bioactive chemicals, including toxins, enzymes, activators, growth factors, and inhibitors.[4, 5] A typical local reaction is characterized by pain and swelling that persists for more than 24-48 hours and resolves within 5-10 days.[6] Kinin is the primary cause of pain, where vasoactive amines are responsible for edema, and tissue damage is mediated by enzymes such as phospholipase and hyaluronidase. A localized reaction occurred for this patient, characterized by swelling in the 103 locations of the sting wound.

An excessive quantity of venom can lead to systemic toxin reactions due to multiple stings, ranging from fifty to hundreds or even thousands of stings. The extensive venom stimulates an inflammatory reaction that involves the release of pro-inflammatory cytokines IL-1β, TNF-α, and IL-6, resulting in generalized inflammation and damaging tissues. As a result, chemical mediators such as histamine, leukotrienes, prostaglandins, and thrombocyte activators are released, interfere with the coagulation system, and cause hemoconcentration. Within 24 hours, it may develop into hemolysis, hemoglobinuria, rhabdomyolysis, elevated liver transaminase enzymes, interstitial nephritis, renal insufficiency, and electrolyte imbalances may develop due to rhabdomyolysis.[1] Administering high-dose steroid therapy as the first line of treatment is advantageous in preventing the progression of interstitial nephritis, which can develop in patients with acute kidney injury following a wasp sting.[7, 8]

The management of acute kidney injury resulting from insect stings is similar to the management of acute kidney injury in individuals with pre-existing kidney problems.[9, 10] Hemodialysis is effective in eliminating small-sized substances from the bloodstream. In case of poisoning caused by toxic substances, dialysis may be performed to eliminate toxic substances from the body rapidly. The requirement for dialysis is not determined by the severity of renal impairment in this type of condition. The Acute Dialysis Quality Initiative (ADQI) created the RIFLE method to diagnose and categorize different types of acute kidney problems.[11] In this patient, a reduction in eGFR to 15 (mL/min/1.73m^2) was observed on the second day as well as the production of urine is less than 0.1 mL per kilogram of body weight per hour.

The appropriate timing to start Renal Replacement Therapy (RRT) in patients with acute kidney injury cannot be ascertained. The initiation of RRT is primarily determined by the clinical manifestation of excessive fluid accumulation and the biochemical indication of an imbalance in solute levels (such as hyperkalemia and severe acidosis).[11] Several studies have shown that initiating dialysis early when there are signs of renal function decline can effectively improve kidney function and patient prognosis and potentially save numerous lives.[7,9] Most patients who experience acute kidney injury due to wasp stings require temporary RRT until their clinical condition improves and their kidney excretory function is restored to its normal state.[12] Metabolic acidosis in patients with acute kidney injury would normally be resolved by administering bicarbonate and rarely requires urgent dialysis unless there is simultaneous volume overload or uremia. When deciding to stop RRT in patients with acute kidney injury, it is important to consider the goal of improving kidney function. The decision whether or not to stop RRT is determined by urine production.[11] The patient decided on RRT, specifically hemodialysis, soon after discovering a significant decrease in kidney function accompanied by

relevant clinical problems. During the patient's stay, hemodialysis was performed in 5 sessions. The interval between hemodialysis sessions was not uniform but instead adjusted according to the patient's clinical status. The patient experienced a reduction in edema anasarca, leading to a decrease of 6 kg in body weight during treatment. While in the hospital, the patient was administered sodium bicarbonate intravenously and then orally to treat metabolic acidosis.

Diuretics are frequently used in the management of patients with AKI to control fluid imbalance. Furthermore, oliguric acute kidney injury is associated with a more adverse outcome compared to non-oliguric acute kidney injury. Consequently, physicians frequently use diuretics to convert oliguric acute kidney injury to non-oliguric acute kidney injury. Diuretics are used to control fluid imbalance and facilitate the administration of nutrition and drugs. Moreover, diuretics have renoprotective effects that can prevent the development of acute kidney injury and accelerate the process of recovery.[11] The patient's condition, marked by the presence of edema anasarca, pulmonary edema, and anuria since admission, suggests the need for intravenous furosemide treatment to promote diuresis. The patient had anuria, with urine production less than 0.1 mL per kilogram per hour for 7 days. Throughout the first 10 days of treatment, the patient's urine output over 24 hours consistently remained below 400 mL. Following four hemodialysis treatments, the patient's kidney function started to improve on the 11th day of therapy. This recovery continued until the patient was discharged with a consistent increase in urine volume and eGFR. After the medical care, the patient's urine increased to a total volume of 3100 mL. Diuretics were administered continuously throughout until the patient was discharged from the hospital. The edema anasarca consistently reduced, with an average weight loss of 0.3 kg per day during the first 7 days and 0.5 kg per day during the subsequent 8 days.

Conclusion

This case illustrates the essential effect of promptly receiving medical treatment following an enormous wasp sting on the patient's prognosis. Initiating dialysis promptly is crucial for rapidly eliminating toxins and thus preserving renal function. Furthermore, the administration of high-dose steroids as an initial treatment has been scientifically proven to be effective. The management of cases involving numerous wasp stings can be effectively managed due to the improvements in healthcare services.

Declarations

Competing interests

The authors declare no conflict of interest.

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