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The Relationship of Hematocrit and Thrombocyte Values with Arteriovenous Fistula Failure in Kidney Failure Patients Undergoing Hemodialysis at Prof. Dr. IGNG Ngoerah Hospital

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ABSTRACT

Background: Chronic kidney failure is still an urgency in today's public health developments. Hemodialysis therapy is still the first choice as a therapy for chronic kidney failure with the use of arteriovenous fistula access as its vascular access. Increased hematocrit and platelet values are one of the factors that affect the failure rate of arteriovenous fistula. In this condition, the authors are interested in examining the relationship between hematocrit and platelet values on arteriovenous fistula failure in renal failure patients undergoing hemodialysis. ***Objective:*** To determine the relationship between hematocrit and platelet values with arteriovenous fistula failure in renal failure patients undergoing hemodialysis. ***Methods:*** This study used a retrospective observational design, with an analytic cross-sectional design to assess the relationship between hematocrit and platelet values and arteriovenous fistula failure in renal failure patients undergoing hemodialysis involving 31 samples of patients undergoing hemodialysis therapy with arteriovenous fistula access at Prof. Dr. General Hospital. I.G.N.G. Ngoerah Denpasar in the period January 2021 – January 2022. ***Results:*** Hematocrit and platelet values were significantly correlated with arteriovenous fistula failure on hemodialysis with a hematocrit OR value of 6.7 (p: 0.025) and a platelet OR value of 15.3 (p: 0.006) indicating that the incidence of arteriovenous fistula failure increased with increasing hematocrit and platelet values. ***Conclusion:*** Arteriovenous fistula failure on hemodialysis is associated and significantly correlated with increased hematocrit and platelet values in patients.

Keywords: kidney failure; arteriovenous fistula; hematocrite; platelet

INTRODUCTION

Chronic kidney disease (CKD) represents a critical global public health challenge, with an estimated global prevalence of around 13.4% [1]. The condition not only contributes significantly to morbidity and mortality but also places a substantial economic burden on healthcare systems worldwide. In Indonesia, CKD prevalence varies by region, with higher rates observed in certain areas, as reported by the 2018 Basic Health Research [2]. This variation underscores the complexity of managing CKD, particularly in developing countries where limited access to dialysis centers exacerbates the situation.

CKD is often associated with other non-communicable diseases such as diabetes mellitus, hypertension, and obesity, further complicating its management and increasing mortality rates [3].

As CKD progresses, patients often require dialysis, with hemodialysis being the most commonly chosen method. This process typically involves the use of an arteriovenous (AV) fistula, which is considered the best vascular access option for hemodialysis due to its association with a higher quality of life and lower complication rates compared to other methods like AV grafts or central venous catheters.

An AV fistula is a surgically created connection between an artery and a vein, designed to facilitate the increased blood flow necessary for effective hemodialysis [4,5].

However, despite the advantages of AV fistulas, they are not without their challenges. High failure rates, limited usability over time, and the potential for complications such as stenosis (narrowing of the blood vessels) and thrombosis (blood clots) are significant concerns. The failure rates of AV fistulas can vary widely, with studies reporting rates ranging from 20% to 60% depending on the population and healthcare setting. This variability highlights the need for a better understanding of the factors contributing to AV fistula failure % [6,7].

Research has indicated that certain hematological factors, particularly hematocrit and platelet levels, may play a role in the success or failure of AV fistulas. High hematocrit levels, for instance, are associated with increased blood viscosity, which can lead to thrombosis—a common cause of AV fistula failure. Similarly, platelet levels are crucial in the blood clotting process, and abnormalities in platelet count or function can increase the risk of thrombosis and subsequent AV fistula failure. However, the relationship between these factors and AV fistula outcomes is complex and remains a subject of ongoing research [8].

In Indonesia, studies examining the relationship between hematocrit and platelet levels and AV fistula failure are still relatively limited. Furthermore, existing research presents conflicting findings, with some studies showing a significant correlation between these factors and AV fistula failure, while others do not 0). Given the potential clinical and theoretical importance of understanding these relationships, this study aims to explore the association between hematocrit and platelet levels and the incidence of AV fistula failure in CKD patients undergoing hemodialysis at Prof. dr. Ngoerah General Hospital Denpasar.

The significance of this research lies in its practical implications for patient care. The tests required to measure hematocrit and platelet levels are relatively simple and cost-effective, making them accessible in most healthcare settings. By identifying patients at higher risk of AV fistula failure, healthcare providers can take preventive measures to improve patient outcomes. This study is therefore not only feasible but also of considerable importance, offering the potential to enhance the management of CKD patients and reduce the complications associated with hemodialysis.

METHOD

The type of research conducted is a retrospective observational study, with an analytic cross-sectional design to assess the relationship between hematocrit and platelet levels with the incidence of arteriovenous (AV) fistula failure in patients with kidney failure. The study was conducted at the Hemodialysis Unit of RSUP Prof Dr. I.G.N.G. Ngoerah, Denpasar, between January 2021 and January 2022.

The inclusion criteria for this study are 1) Patients with stage V chronic kidney failure; 2) Patients receiving hemodialysis therapy with AV fistula access; and 3) Patients aged 18 years or older. The exclusion criteria for this study are 1) Incomplete medical record data; 2) Pregnant women; 3) Foreign nationals.

Data analysis was performed using SPSS for Windows version 21.0 software. The statistical analyses conducted include univariate analysis, bivariate analysis, and multivariate analysis.

RESULT

This study involved the medical records of 31 patients who had undergone hemodialysis therapy through AV fistula access. The characteristics of the subjects in this study were described based on age, gender, body mass index (BMI), history of hypertension, history of diabetes mellitus (DM), and the location of AV fistula access. The results are presented in Table 1.

TABLE 1: Characteristics of Study Subjects.

Characteristics	Fistula Access Failure	
	Failed (n=11)	Successful (n=20)
Age (mean±SD)	58.27±8.88	54.65±16.29
Gender (n, %)		
Man	3 (9.7%)	11 (35.5%)
Woman	8 (25.8%)	9 (29%)
BMI		
Overweight (≥ 23 kg/m2)	4 (12.9%)	11 (35.5%)
Normal (18.5 – 22.9 kg/m2)	7 (22.6%)	9 (29%)
Hypertension (n, %)		
Yes	7 (22.6%)	8 (25.8%)
No	4 (12.9%)	12 (38.7%)
DM disease (n, %)		
Yes	4 (12.9%)	10 (32.3%)
No	7 (22.6%)	10 (32.3%)
Fistula access location (n, %)		
Radiocephalic	6 (19.4%)	16 (51.6%)
Braciocephalica	5 (16.1%)	4 (12.9%)

Table 1 shows that the average age of patients who experienced AV fistula failure during hemodialysis therapy was 58.27 years (SD: 8.88), while those who succeeded had an average age of 54.65 years (SD: 16.29). In terms of gender, the incidence of AV fistula failure was higher in females (25.8%) compared to males (12.9%). Based on BMI, the incidence of AV fistula failure was higher in patients with a normal BMI (22.6%) compared to those who were overweight (12.9%).

Regarding the history of hypertension, a higher incidence of AV fistula failure was observed (22.6%), and concerning the history of DM, AV fistula failure occurred more frequently in patients without a history of DM (22.6%). The incidence of AV fistula failure based on location was higher in the radio cephalic site (19.4%) compared to the brachiocephalic site (16.1%). The characteristics of the study variables are described in Table 2.

TABLE 2: Characteristics of Study Variables.

Characteristics	Fistula Access Failure	
	Failed (n=11)	Successful (n=20)
Hematocrit Value (mean±SD)	50.37±13.5	35.4 ± 10.94
Platelet Values (mean±SD)	406,545.45 ± 91520.88	278,900±66382

Table 2 shows that a higher hematocrit value was associated with AV fistula failure, with an average of 50.37 compared to a successful outcome with an average hematocrit value of 35.4. A higher platelet count was also associated with AV fistula failure, with an average of 406,545.45 compared to a successful outcome with an average platelet count of 278,900.

Bivariate analysis aimed to determine the relationship between age, gender, BMI, hypertension, history of DM, and the location of AV fistula access, hematocrit value, and platelet count with the occurrence of AV fistula failure. The results of the analysis using a 2x2 table are presented in Table 3.

TABLE 3: Bivariate Analysis.

Variables	Fistula Access Failure		OR	IK 95%	*p*
	Fail	Succeed			
Hematocrit Value (n, %)					
High ≥30%	9 (29%)	8 (25.8%)	6,7	1.14-39.79	0.025
Low <30%	2 (6.5%)	12 (38.7%)			
Platelet Value (n, %)					
High ≥400,000/µL	5 (16.1%)	1 (3.2%)	15.3	1.53-163.54	0.006
Normal <400,000/µL	6 (19.4%)	19 (61.3%)			

Table 3 shows that a high hematocrit value (≥30%) was associated with AV fistula failure (29%) more frequently than a low hematocrit value (<30%) (6.5%). Statistically, there was a significant relationship between hematocrit value and AV fistula failure, with a p-value of 0.025 < 0.05. The odds ratio (OR) was 6.7, indicating that a high hematocrit value (≥30%) increased the likelihood of AV fistula failure by 6.7 times. A high platelet count (≥400,000/µL) was associated with AV fistula failure in 5 respondents (16.1%), while only 3.2% of those who succeeded had a high platelet count. Statistically, there was a significant relationship between platelet count and AV fistula failure, with a p-value of 0.006 < 0.05. The OR was 15.3, indicating that a high platelet count increased the likelihood of AV fistula failure by 15.3 times.

Multivariate analysis aimed to determine the influence of independent variables when tested together. Multivariate analysis in this study was conducted using logistic regression. The omnibus test results showed a p-value of 0.007, and the Hosmer and Lemeshow test results showed a p-value of 0.320, indicating that the model used was fit. The classification table showed an accuracy of 87.1%, meaning that the model used could predict the variables of age, gender, BMI, hypertension, DM, access location, hematocrit, and platelet count with an accuracy of 87.1%. The final results of the variables in the equation are presented in Table 4.

TABLE 4: Multivariate Analysis Results.

Variable	B	OR	IKI 95%	*p*
Age ≥ 50 years	0.608	1.8	0.07-43.98	0.707
Male gender	-0.298	0.7	0.04-13.52	0.841
BMI overweight	-2,085	0.1	0.00-2.21	0.156
There is hypertension	4,721	112.3	0.79-15845.33	0.062
There is DM	-2,620	0.0	0.00-5.04	0.226
Location of radiocephalic AV fistula	0.651	1.9	0.08-45.39	0.687
Hematocrit value ≥ 30%	4,680	107.7	1.14-10170.72	0.044
Platelet value ≥ 400,000/µL	3,666	39	1.44-1059.56	0.029

Table 4 shows that hematocrit and platelet values had a dominant influence on the occurrence of AV fistula failure compared to the variables of age, gender, BMI, history of hypertension, history of DM, and location of AV fistula access. Hematocrit and platelet values had positive B values, indicating a positive relationship between hematocrit and platelet levels and AV fistula failure. Hematocrit had an adjusted OR of 107.7 (95% CI: 1.14-10170.72), which was higher than that of platelets with an adjusted OR of 39 (95% CI: 1.44-1059.56). The multivariate analysis concluded that hematocrit had a dominant influence on the occurrence of AV fistula failure, increasing the likelihood of AV fistula failure by 107.7 times. This result was followed by a stepwise multivariate analysis of hypertension, hematocrit, and platelet count. The analysis results are presented in Table 5.

TABLE 5: Multivariate Analysis Results.

Variable	B	OR	IKI 95%	*p*
History of Hypertension	2,188	8.9	0.87-90.59	0.064
Hematocrit value ≥ 30%	3,126	22.7	1.44-359.89	0.026
Platelet value ≥ 400,000/µL	3,282	26.6	1.79-395.61	0.017

Table 5 shows that hematocrit and platelet values had a dominant influence on the occurrence of AV fistula failure compared to the variable of hypertension. Hematocrit and platelet values had positive B values, indicating a positive relationship between hematocrit and platelet levels and AV fistula failure. Hematocrit had an adjusted OR of 22.7 (95% CI: 1.44-359.89), which was lower than that of platelets with an adjusted OR of 26.6 (95% CI: 1.79-395.61). The multivariate analysis concluded that platelet count had a dominant influence on the occurrence of AV fistula failure, increasing the likelihood of AV fistula failure by 26.6 times.

DISCUSSION

The results of the study showed that the average age in the group that experienced failure was 58.27 years (SD: 8.88), while the group that succeeded had an average age of 54.65 years (SD: 16.29). In terms of gender, the incidence of AV fistula access failure was higher in females (25.8%) compared to males (12.9%). Kartikasari et al. (2020) found that the incidence of CKD was higher in females (51%) but with a lower average age of 49.7 years [9]. A similar finding was reported by Ge, Fang, and Rao (2022), where females were more frequently found with AV fistula failure [10].

The average age of CKD patients in this study aligns with the study by Chen et al. (2015), which found an average age of 54.6 years. Generally, the aging process also plays an important role in the pathophysiology of CKD, where GFR declines with age, and CKD can accelerate vascular aging and atherosclerosis [11]. This leads to increased arterial stiffness and a higher risk of developing systolic hypertension in elderly patients with CKD [12]. A different result was found in the study by Sichona et al. (2023), where the majority were males, with a male-to-female ratio of 4.2:1, but the age range was almost the same, with an average of 54.1 years [13]. Similarly, the study by Wicaksana et al. (2022), which involved 34 patients, found that 61.8% were males, with an average age of 52.62 years [14].

Based on BMI, the incidence of AV fistula access failure was higher in patients with normal BMI (22.6%) compared to those who were overweight (12.9%). In obesity, there are reports of sodium excretion disorders, increased sympathetic nervous system activity, and RAAS activation [12,15]. Obesity has also been associated with a lower rate of arteriovenous access maturation within 180 days and a higher rate of reintervention. Perioperative outcomes and 30-day primary patency were not significantly related to patient BMI [16]. Long-term use of AV fistula has a higher failure rate in obese patients than in non-obese patients, but statistically, there is no difference between overweight patients and those with normal BMI [17]. Obesity is also associated with reduced fistula maturation linked to lower patency, but higher BMI is associated with better patient survival rates. Obese patients with CKD are more likely to have arteriovenous fistula placement at the onset of hemodialysis [18].

Based on the history of hypertension, the incidence of AV fistula access failure was higher (22.6%). The study by Ge, Fang, and Rao (2022) found that the percentage of hypertension-related AV fistula failure was 17.1% [10]. The study by Gasparin et al. (2022) also found no relationship between hypertension and AV fistula failure [19]. Hypertension can cause and accelerate kidney injury when autoregulation disorders allow the transmission of high systemic pressure to the glomeruli, resulting in glomerulosclerosis. Kidney injury and decreased GFR, in turn, can lead to hypertension due to impaired sodium excretion and increased sensitivity to sodium regulation [12]. The creation of an AVF significantly lowers blood pressure in patients with end-stage kidney disease, while blood pressure tends to rise after ligation. This illustrates that the hemodynamic consequences of AVF should be considered, especially in severe hypertension. The connection between arteries and veins usually increases cardiac output, ventricular work, and venous return to the heart [20].

The incidence of AV fistula access failure was found to be higher in patients without a history of diabetes mellitus (12.9%). This contrasts with the findings of Ge, Fang, and Rao (2022), who found that the percentage of DM-related AV fistula failure was 25.71% [10]. The study by Gasparin et al. (2022) found no relationship between DM and AV fistula failure [21].

Hyperglycemia in diabetes mellitus can also contribute to the worsening of CKD. Hyperglycemia causes an increased amount of glucose to be rapidly filtered through the glomerular filtration barrier, inducing hyper-reabsorption of glucose in the proximal tubules. Hyper-reabsorption of glucose involves the induction of glucose transporter expression and a massive increase in energy-consuming transport processes in proximal tubule cells, increasing oxygen demand in the renal cortex and outer medulla, which induces relative ischemia and increases the expression of cellular stress markers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM1). The increased workload of the proximal tubule leads to hypertrophy and elongation of the proximal tubule, contributing to kidney hypertrophy [22].

The incidence of AV fistula access failure based on location was found to be higher in the radiocephalic site (19.4%) compared to the brachiocephalic site (16.1%). A different finding was reported by Sichona et al. (2023), where AV fistula was more frequently located in the brachiocephalic site, but there was no relationship between the location of the AV fistula and its maturation [23]. However, the study by Gasparin et al. (2022) found a relationship between the location of the fistula and AV fistula failure [21].

Hematocrit values were found to be higher in cases of AV fistula access failure, with an average of 50.37, compared to successful cases, which had an average hematocrit value of 35.4. The study by Ge, Fang, and Rao (2022) reported different results, with an average hematocrit of 34.91 in AV fistula failures, while successful cases had an average hematocrit of 28.19 [10]. Platelet values were also found to be higher in cases of AV fistula access failure, with an average of 406,545.45, compared to successful cases, which had an average platelet value of 278,900. The study by Ge, Fang, and Rao (2022) found different results, with an average platelet count of 205.87 in AV fistula failures, compared to 218.93 in successful cases [10]. Usman et al. reported that there was no significant difference in the average platelet count between patients who experienced AV fistula failure and those with patent AV fistulas (229 ± 75 ×103/µL versus 258 ± 79 ×103/µL, p = 0.061) [24].

The AV fistula failure rate in this study was 35.5%, consistent with the reports by Al-Jaishi et al. (2014) and Satrio, Yasa & Widiana (2020) [25,26], who found an AV fistula failure rate of 35.9%, with the majority classified as late failure, with a primary patency rate of 60% [25,26]. The incidence of primary failure in arteriovenous fistulas was reported to be quite high, at 23% [25,26]. The AV fistula failure rate was 29.5% at RSUP Prof Dr. I.G.N.G. Ngoerah in 2019 [27]. The study by Wicaksana et al. (2022) found a prevalence of AVF failure of 32.4% (n=11) [28].

The study by Ryandi, Yasa, and Widiana (2020) showed a relationship between hemoglobin levels and AVF failure. Hemoglobin levels, along with PTT and APTT levels, are also said to play a role in AVF failure, although the mechanism remains unclear. Patients with hemoglobin levels < 8 g/dl in CKD patients are at higher risk. Studies have shown that correcting hemoglobin levels in hemodialysis patients offers many benefits, with a target hemoglobin level between 10 g/dl and 12 g/dl [25].

In an ideal situation, patients should be referred for surgery several months before starting HD. A detailed medical history, including the presence of diabetes, hypertension, peripheral ischemia, amputations, coronary or carotid surgery, pacemakers, stroke, central venous cannulation, and physical examination of both extremities, is essential. Pulse, Allen test, deep and superficial venous patency should be checked. According to current guidelines, preoperative DUS should be performed, and if possible, vein mapping should also be conducted. Some authors recommend that the DUS evaluation be performed by the surgeon constructing the AVF [29,30].

Many authors agree that surgical skill is an important factor influencing the success of AVF surgery [31–33]. Surgical experience is a statistically significant predictor of success in access surgery [34]. Inadequate surgical experience contributes to AVF failure [35]. The surgeon's decisions and skills are crucial to the success of access [32]. However, in this study, the researcher did not evaluate the operator's factors because the study was based on medical records with retrospective data.

Several studies have mentioned that arterial and venous diameters below 2 mm are predictors of a high incidence of early thrombosis or failure to mature, and some authors recommend setting cut-off sizes for arteries and veins. The most frequently mentioned recommendations are an arterial diameter ≥ 2 mm and a venous diameter ≥ 2.5 mm or a venous diameter ≥ 3 mm [36–38]. Several studies also emphasize that vascular compliance is more important than vessel diameter [39,40]. The predictive value of the arterial resistance index for the success of AV fistulas has not yet been confirmed in a single study, where preoperative arterial resistance > 0.7 indicates that arterial blood flow will not increase sufficiently, thereby reducing the likelihood of AVF success [41]. The variation in venous diameter in the forearm should be considered when defining the diameter cut-off before vascular access surgery [42].

The study found a relationship between hematocrit levels and AV fistula access failure. A high hematocrit value (≥30%) was associated with AV fistula access failure (29%) more frequently than a low hematocrit value (<30%) (6.5%). A high hematocrit value (≥30%) increased the likelihood of AV fistula access failure by 6.7 times. The multivariate analysis found that hematocrit had an adjusted OR of 107.7 (95% CI: 1.14-10170.72). Hematocrit had a dominant influence on the occurrence of AV fistula access failure compared to age, gender, BMI, history of hypertension, history of DM, fistula location, and platelets.

A similar multivariate result was also found in the study by Ge, Fang, and Rao (2022), indicating that hematocrit has a dominant influence [10]). The study by Wicaksana et al. (2022), which involved 34 patients, also found a relationship between hematocrit levels and AVF failure in hemodialysis patients [28] Patients with hematocrit levels below 33% were mostly successful in AV fistula creation (74.2%), while eight patients experienced failure with hematocrit levels below 33%, and more than 36% experienced AVF failure.

Consistent results were also found in the study by Satria et al. (2020), where the majority of patients with hematocrit levels below 33 had successful AVF procedures (70.4%), with only a small proportion of patients with hematocrit levels below 33 experiencing AVF failure, while all patients with hematocrit levels between 33-36% experienced AVF failure (100%) [43]. Thus, there is a significant relationship between hematocrit levels and AVF failure in hemodialysis patients. The study by Gasparin et al. (2022) also found a relationship between hematocrit levels and AV fistula failure [21].

Hematocrit is known to provide a fairly accurate description related to the reduction in red blood cell count in chronic kidney disease (CKD). However, the relationship between kidney function levels and hematocrit reduction is not yet fully understood [44,45]. Furthermore, Hsu et al. (2001) reported that the average hematocrit value decreases with a decrease in creatinine clearance to <60 ml/min in men and <40 ml/min in women, with a greater reduction in hematocrit observed in men compared to women. Individuals with lower GFR have lower baseline hematocrit values and experience a decrease in hematocrit with changes in GFR [44]. GFR <45 ml/min/1.7 m^2, male gender, and younger individuals or those with proteinuria are at risk of experiencing hematocrit reduction related to decreased GFR [11].

High hematocrit levels are associated with thrombosis and increased blood viscosity, which disrupts blood flow. Blood viscosity related to hematocrit affects the interaction between platelets and blood vessel surfaces. In blood flow, platelet adhesion increases with increasing hematocrit. Thus, the erythrocyte volume fraction influences hemostasis and thrombosis. Hematocrit and platelets are selected due to the ease of their measurement compared to monitoring with Doppler ultrasound, which cannot be used in every dialysis session [46].

Hematocrit levels in CKD patients are also affected by hemodialysis therapy. Kartikasari et al. (2020) mention that after hemodialysis with ultrafiltration ≥ 2 liters, there is an increase in hemoglobin, platelets, and hematocrit. Hemodialysis causes changes in the hemorheological profile and results in a significant increase in hematocrit, thereby increasing blood viscosity [9]. Hematocrit is a strong predictor of complications and cardiovascular mortality in kidney disease patients [47].

Increased hemoglobin can raise the incidence of cardiovascular events and AV fistula emboli due to increased blood viscosity. As a result, there is an increased risk of AV fistula failure [10]. Adjusting erythropoietin doses in CKD patients with anemia, gradually increasing hemoglobin levels, and maintaining hemoglobin at levels important for preventing AV fistula emboli [10].

Various studies indicate a relationship between higher hematocrit values and the incidence of thrombosis. The incidence of thromboembolism is significantly higher in patients with increased hematocrit, whether in primary erythrocytosis conditions (e.g., polycythemia vera) or secondary erythrocytosis conditions (e.g., Eisenmenger syndrome, cyanotic congenital heart disease, and living at high altitudes) [48]. Brækkan found that every 5% increase in hematocrit value results in a 1.25-fold higher risk of venous thromboembolism [49].

Higher hematocrit values indicate thicker blood, where this increased blood thickness can lead to disrupted blood flow. Disrupted blood flow is one of the components of the Virchow triad underlying the mechanism of thrombosis in AV fistula failure. Hematocrit, or the percentage of red blood cell volume in the total blood volume, is closely related to disrupted blood flow in the Virchow triad. Increased hematocrit can cause increased blood viscosity and stimulate blood clotting activation, accelerating thrombosis formation [50]. High hematocrit levels can also increase platelet aggregation, blood viscosity, and venous stasis, leading to a state of hypercoagulability. The thrombosis mechanism in high hematocrit is thought to occur because platelets are more likely to be pushed against the blood vessel walls, increasing the likelihood of platelet adhesion to collagen and vWF, and activating the coagulation pathway. Additionally, a higher number of red blood cells or thicker blood increases the chances of vessel injury (high shear condition), which activates endothelial cells and leukocytes. This leukocyte and endothelial activation also leads to platelet activation and increases platelet adhesion, forming leukocyte-platelet bonds. These leukocyte-platelet bonds amplify further platelet activation through the release of cathepsin G and tissue factor, resulting in fibrin clot formation [51]. Therefore, it can be concluded that thrombosis events that generally occur in AV fistula failure can be caused by high erythrocyte volume fraction or hematocrit [25,50].

Research results indicate a relationship between platelet values and AV fistula failure. High platelet values ≥ 400,000/µL are associated with AV fistula failure (16.1%) and successful cases only 3.2%. High platelet levels increase the risk of AV fistula failure by 15.3 times. Jain et al. (2021) state that CKD patients have a 16% higher risk of experiencing cardiovascular thrombotic events such as myocardial infarction or ischemic stroke. The mechanism causing these clinical events is increased platelet activation and inflammation due to CKD, making CKD patients 10 times more likely to experience bleeding compared to the normal population [52].

Different results were found in Wicaksana et al. (2022), which involved 34 patients and found no relationship between platelet values and AVF failure, with a p-value of 0.411 [28]. Similarly, Satria et al. (2020) found no significant relationship between platelet levels and AVF failure in dialysis patients. Platelets play a crucial role in primary hemostasis, where high platelet levels are associated with slowed blood flow and the development of coagulation factors that can increase thrombosis risk. Satria et al. (2020) demonstrated that at platelet values <150,000, 150,000-400,000, and 400,000, AV fistula failure occurred in 0, 9, and 5 individuals, respectively [53]. Lano et al. (2019) found a significant relationship between mean platelet volume (MPV) and AV fistula failure (p=0.001, OR=1.58) in 153 hemodialysis patients in France [46]. MPV reflects the average platelet size in the blood sample and is a potential marker for platelet activation and function. Another study in Turkey reported a significant relationship between the platelet-lymphocyte ratio (PLR) and AV fistula failure with a p-value of 0.001 [54]. A case-control study of 50 hemodialysis patients in Egypt showed a significant relationship between MPV/platelet ratio with a cut-off level of 53.7, consistent with a study of 143 patients in South Korea with a p-value of 0.001 [55,56]. However, other research also found no significant relationship between platelets and AV dysfunction (p=0.323), possibly due to other factors influencing AV fistula dysfunction [53].

The increased bleeding risk in CKD patients is associated with dysfunction of coagulation factors, platelet function, platelet aggregation, and interactions between platelets and blood vessel walls. CKD patients also experience a prothrombotic condition due to disturbances in the ratio of coagulation factors and inhibitors, decreased fibrinolytic activity, platelet hyperactivity, and endothelial dysfunction [57]. CKD patients may experience thrombocytopenia due to inadequate production by megakaryocytes or persistent platelet activation due to repeated hemodialysis [58]. A reduction in platelet count of about 20% can occur in CKD stage 5 patients [59].

Platelet dysfunction in CKD results from intrinsic defects in platelets, including impaired platelet adhesion and abnormal interactions between platelets and the endothelium [60]. Under normal conditions, platelets adhere to the vascular endothelium through von Willebrand factor (vWF) receptors and collagen complexes (GPIb-V-IX and GPVI, as well as integrin α2β1), aggregate (through fibrinogen binding with GPIIb/IIIa), and release their granule contents (including ADP, serotonin, and thromboxane A2). This entire process is essential for proper hemostatic function [61]. Platelet adhesion to the vascular endothelium occurs via vWF receptors and collagen complexes (GPIb-V-IX) [60,61]. Platelet adhesion to the subendothelial surface then activates another glycoprotein receptor, GPIIb/IIIa, which binds with fibrinogen [60].

Activated platelets release their granule contents (ADP and serotonin). The release of ADP and serotonin potentiates platelet activation and increases platelet recruitment to form platelet aggregates. The vascular endothelium also responds to platelet activation by releasing nitric oxide (NO) and prostacyclin (PGI2) to inhibit further platelet reactivity and modulate endothelial response. NO increases platelet levels of cyclic guanylyl monophosphate (cGMP) and reduces platelet aggregation on collagen. Simultaneously, PGI2 increases cyclic adenosine monophosphate (cAMP) levels in platelets, leading to decreased platelet reactivity to various agonists, inhibition of platelet shape change, and vasodilation [61].

In CKD patients, levels of ADP and serotonin in platelet granules are reduced, and adenosine triphosphate (ATP) release in response to thrombin is also decreased [57,60]. In addition to ADP and serotonin, platelets in uremic patients also contain less thromboxane A2, leading to reduced platelet adhesion and aggregation [57,61]. Thromboxane A2 is synthesized by platelets in response to ADP, collagen, thrombin, and arachidonic acid. This synthesis is reduced in CKD patients [60]. Uremic patients also show decreased levels of GP1b, likely due to proteolytic damage to GP1b expressed on the platelet surface. Additionally, the binding between vWF and fibrinogen on GPIIb/IIIa is reduced in uremic patients, leading to impaired platelet adhesion to the subendothelium [60]. vWF primarily binds to GPIb-IX-V and mediates platelet adhesion, while fibrinogen primarily binds to GPIIb/IIIa and mediates platelet aggregation [57].

CKD patients experiencing uremia are at risk of thrombosis due to systemic metabolic abnormalities that disrupt the balance of thrombotic and antithrombotic factors in the circulatory system. Additionally, there is an increase in fibrin levels and prothrombin inactivation, directly causing a hypercoagulable state [62]. Generally, CKD patients have elevated levels of D-Dimer, CRP, fibrinogen, factor VII, factor VIII, and vWF. This elevation is thought to be due to increased synthesis relative to its excretion through urine. Conversely, levels of factor IX, XI, and XII are lower due to increased urinary excretion [63]. Other factors, such as adhesion molecules like intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin, which are associated with platelet hyperactivity, are also found to be elevated in CKD patients [57,62,64].

Dialysis in CKD patients has been found to facilitate platelet activation and lead to a hypercoagulable state. The semi-permeable membranes used in dialysis machines can activate platelets and increase levels of P-selectin, vWF, and D-dimer. Additionally, repeated punctures during dialysis can trigger local inflammation in the endothelial lumen [62]. In uremic patients, increased levels of P-selectin have been observed.

Platelets with P-selectin on their surface can conjugate with monocytes and neutrophils through the glycoprotein P-selectin ligand-1 (PSGL-1). This conjugation affects leukocyte reactivity and exacerbates inflammation and thrombosis. Furthermore, P-selectin also enhances the formation of platelet-erythrocyte aggregates in CKD patients, particularly those undergoing dialysis [57].

Thrombosis and stenosis in arteriovenous (AV) fistulas are commonly associated with inflammatory conditions, circulatory system abnormalities, and hemostatic dysfunction. Platelets play a crucial role in primary hemostasis, where high platelet counts are associated with slower blood flow and increased development of coagulation factors, thereby raising the risk of thrombosis, with hyperplasia of the intima being a key pathophysiological factor.

Platelets are involved in intimal hyperplasia, including shear stress (WSS), hypoxic injury, inflammation, uremia, and thrombosis [65]. Satria (2020) studied inflammatory activity as a dominant cause of AV fistula failure during hemodialysis, finding that high platelet counts can slow blood flow and stimulate coagulation factors, leading to stenosis or thrombus formation in the AV fistula anastomosis [66]. Intimal hyperplasia is defined as the abnormal migration and proliferation of vascular smooth muscle cells in response to vascular injury and is triggered by inflammatory responses. Large platelets with high mean platelet volume (MPV) contain denser α-granules, aggregate more rapidly after collagen stimulation, and can secrete platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), fibrinogen, and beta-thromboglobulin. PDGF and TGF-β are two well-known factors involved in initiating intimal hyperplasia. PDGF is a growth factor involved in the development of intimal hyperplasia and stimulates the mobilization, migration, and proliferation of inflammatory cells in smooth muscle cells. TGF-β is a pro-inflammatory cytokine involved in the development of atherosclerotic plaques. PDGF and TGF-β are found in large amounts in the intima of stenosed AV fistulas [67,68]. Additionally, platelets play a crucial role in initiating thrombosis, and activated platelets can increase thrombotic risk. Higher platelet aggregation has been reported in patients with AV dysfunction [68].

The most commonly used platelet markers in research are mean platelet volume (MPV) and the platelet-to-lymphocyte ratio (PLR). MPV is a measurement performed by automated blood analyzers using electrical impedance or optical fluorescence methods. MPV reflects the average size of platelets in a blood sample and is a potential marker of platelet activation and function [54]. Other markers like PLR can also be used to indicate systemic inflammation more specifically [54].

A study by Lano et al. (2019) on 153 dialysis patients in France demonstrated a significant relationship between MPV and AV fistula failure (p=0.001, OR=1.58). Among the 153 patients, 54 experienced AV fistula dysfunction, with those having the highest MPV reported to be at the highest risk of AV fistula dysfunction. MPV can also be used as a predictor of AV fistula failure with an OR of 1.52 [46]. In another study in Turkey, PLR was reported to have a significant relationship with AV fistula failure with a p-value of 0.001, although the correlation between PLR and the degree of stenosis was not found, making its use as a predictor considered unreliable. Nonetheless, an increased PLR can alert clinicians to further evaluate AV fistula dysfunction using Doppler ultrasound [54]. Similarly, Pasqui et al. found that higher PLR ratios were associated with higher rates of AV fistula failure, with a cutoff value of PLR >208.28 showing 61.84% sensitivity and 56.86% specificity in predicting AV fistula failure [69].

Another case-control study of 50 patients undergoing hemodialysis in Egypt found a significant relationship between MPV/platelet with a cutoff level of 53.7. MPV/platelet values can predict AV fistula failure with 100% sensitivity and 84% specificity [56]. This result is consistent with another study of 143 patients in South Korea with a p-value of 0.001 [55]. Another case-control study by Ge et al. also showed a relationship between platelet count and AV fistula failure due to obstruction, with patients experiencing AV fistula failure having significantly lower platelet counts compared to those with patent AV fistulas (205.87 ± 34.66 × 10^3/µL vs. 218.93 ± 53.33 × 10^3/µL, p = 0.039). However, the study did not explain why lower platelet counts were associated with a lower rate of AV fistula failure [10]. Gheith et al. demonstrated a significant negative correlation between platelet count and AV fistula patency duration (r = -0.540, p < 0.001), indicating that higher platelet counts lead to faster AV fistula failure. This is likely due to increased thrombosis risk with higher platelet counts, resulting in quicker AV fistula failure [70]. Elwasif et al. found that patients with AV fistula failure had significantly higher MPV (8.05 ± 1.06 vs. 10.09 ± 0.94, p = 0.04), MPV/PL (61.20 ± 3.12 vs. 55.3 ± 4.98, p = 0.01), and PCT (0.211 ± 0.068 vs. 0.201 ± 0.07, p = 0.30) compared to patients with patent AV fistulas. In this study, a cutoff value of MPV/PL ratio of 58.7 had 92.5% sensitivity, 81% specificity, 83% positive predictive value, and 30.5% negative predictive value for predicting AVF dysfunction [71].

CONCLUSION

Based on the research and discussion, it can be concluded that:

- There is a relationship between hematocrit levels and the incidence of arteriovenous (AV) fistula failure in kidney failure patients.
- There is a relationship between platelet levels and the incidence of arteriovenous (AV) fistula failure in kidney failure patients.

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