Risk Factors for Temporary Vascular Access Infection in Patients with End-Stage Renal Disease Undergoing Hemodialysis in Cipto Mangunkusumo Hospital

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ABSTRACT

Background: *Temporary vascular access is used to provide adequate hemodialysis for patients who are initiating dialysis or are awaiting maturation of a more permanent vascular access. However, infection is one of the most frequent complications of using temporary vascular access and is the second leading cause of death in patients undergoing hemodialysis after cardiovascular events. There has been no research on the risk factors for the incidence of infection in patients using temporary vascular access in Indonesia.* ***Methods:*** *This is a retrospective cohort study utilizing secondary data from medical records of 318 subjects aged 18 years and older with end-stage renal disease and undergoing hemodialysis using temporary vascular access at Cipto Mangunkusumo Hospital.* ***Results:*** *Temporary vascular access infection was found in 125 of 318 subjects (39.3%). The risk factors of temporary vascular catheter infection in the multivariate analysis were females (OR 1.731; 95% CI 1.050-2.854; p=0.032), low hemoglobin levels (OR 2.293; 95% CI 1.353-3.885; p=0.002), presence of diabetes mellitus (OR 2.962; 95% CI 1.704-5.149; p<0.001) and duration of catheter insertion (OR 5.322; 95% CI 1.871-15-135; p=0.002). The association between ferritin and catheter insertion site was not analyzed as a risk factor because it was not performed in all subjects.* ***Conclusion:*** *The incidence of infection in patients with end -stage renal disease undergoing hemodialysis using temporary vascular access at Cipto Mangunkusumo Hospital was 39.3%. Female gender, low hemoglobin level, diabetes mellitus, and duration of catheter insertion were risk factors for temporary vascular access infection.*

Keywords: *Risk factors, temporary vascular access infection, end-stage renal disease, chronic kidney disease, hemodialysis.*

INTRODUCTION

Chronic kidney disease (CKD) is a complex condition characterized by decreased kidney function. Patients diagnosed with CKD can survive with the help of renal replacement therapy, one of which is dialysis. Based on the 2016 NKF-KDOQI guidelines regarding CKD, the recommended management for CKD patients includes dialysis through vascular access for hemodialysis. The usage number of hemodialysis catheters as vascular access increases linearly coinciding with the increase in new hemodialysis patients.[1]

A common complication that can occur after installing hemodialysis access is infection. Three factors known to influence the occurrence of bacteremia in hemodialysis patients are patient immunity, bacterial virulence, and hemodialysis procedures. Infections after hemodialysis catheter insertion can cause various complications such as local infection at the exit-site to hemodynamic instability, changes in mental status, and death. Patients undergoing hemodialysis through temporary access have a 2-3 times greater risk of infection and death than those using permanent access.[2]

To date, there have been no studies in Indonesia that explored the risk factors predisposing patients to infection after temporary vascular access placement. By understanding the risk factors associated with infection after hemodialysis catheter insertion, further actions can be undertaken to control the source of infection to reduce the percentage of post-catheter insertion infections in hemodialysis patients.

METHODS

A retrospective analysis was conducted on CKD patients undergoing hemodialysis in Cipto Mangunkusumo Hospital, Jakarta, Indonesia from January 2015 until the required sample size was met. The inclusion criteria for the study were adult CKD patients (aged ≥ 18 years) who underwent hemodialysis with temporary vascular access, either in the femoral, internal jugular, or subclavian vein, and presented with infection. Patients with an infection prior to being diagnosed with an infection related to the insertion of a temporary catheter or infection outside the catheter insertion site, patients with missing data in the medical record, and patients using immunosuppressive drugs or were under medications that decreased the immune system, were excluded from the study.

The data retrieved include patient characteristics such as age, gender, hemoglobin level, albumin level, duration of catheter use, presence of diabetes mellitus, hypertension, heart failure and malignancy, catheter insertion location, culture results, and antibiotics used to treat the infection. The outcome of this study was the incidence of temporary vascular access infection.

Ethical Clearance

The ethical clearance was issued by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital, with approval number KET-1227/UN2.F1/ETIK/PPM.00.02/2020.

Statistical Analysis

The statistical analyses were done electronically using the SPSS software. Data regarding the baseline clinical characteristics of research subjects were presented in tables. Categorical data were presented in percentages. Bivariate analysis was performed using the Chi-square test for nominal variables. In the bivariate analysis of nominal variables, if the Chi-square test conditions were not satisfied, Fisher's exact test or Kolmogorov-Smirnov test was used instead. All the bivariate outcome variables with a $p<0.25$ were included in the multivariate analysis using logistic regression.

RESULTS

From 2607 patients with CKD in need of hemodialysis found in the hospital database, a total of 318 patients were included in this study. The reason for the exclusion of the subjects were patients with an infection before being diagnosed with an infection related to the insertion of a temporary catheter or infection outside the catheter insertion site, incomplete or missing data of patients in the medical record, and patients using immunosuppressive drugs **(Figure 1).**

The characteristics of the included and excluded subjects undergoing hemodialysis with

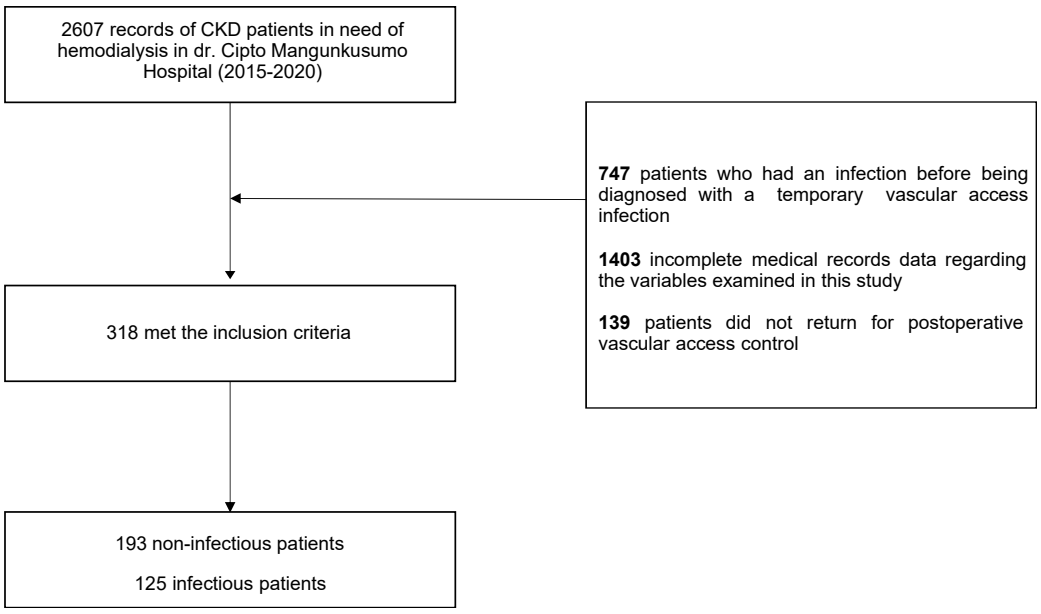

Figure 1. Flow diagram showing the patient selection.

temporary non-tunneled vascular access were not significantly different **(Table 1).** Overall, the included subjects had a mean age of 51.7 years, 160 were males, and 158 were females. The CKD patients with infection had a median age of 54 years (IQR 41-46 years), while those not infected had a median age of 55 years (IQR 46-63 years). Comorbid conditions such as hypoalbuminemia

Table 1. Characteristic comparison of the included and excluded groups.

Variables	Data	
	Included (318)	**Excluded (2289)**
Age (years), Median (IQR)	55 (43-62)	53 (42-61)
Age, n (%)		
≥ 60 years	92 (28,9)	602 (26,4)
< 60 years	22 (71,1)	1682 (73,6)
Gender, n (%)		
Male	160 (50,3)	1155 (50,7)
Female	158 (49,7)	1125 (49,3)
Hemoglobin level, n (%)		
< 10 g/dL	102 (32,1)	965 (44,2)
≥ 10 g/dL	216 (67,9)	1217 (55,8)
Albumin, n (%)		
Hypoalbuminemia (< 3.50 mg/dL)	193 (64,8)	858 (68,0)
Normoalbuminemia (≥ 3.50 mg/dL)	105 (35,2)	403 (32,0)
Ferritin, n (%)		
Low Risk infection (< 3822 µg/L)	108 (100,0)	689 (100,0)
High Risk Infection (≥ 3822 µg/L)	0 (0,0)	0 (0,0)
Duration of catheter use, n (%)		
≥ 30 days	83 (26,3)	364 (26,0)
< 30 days	233 (73,7)	1034 (74,0)
Urea, Median (IQR)	162,5 (111,63-213)	141,8 (105,4-183,0)
Creatinine, Median (IQR)	7,89 (5,56-10,90)	7,10 (4,9-10,90)
eGFR, Median (IQR)	7,85 (5,02-13,0)	8,4 (5,85-11,10)

were found in 64.8% of subjects, followed by diabetes (64.8%), hypertension (64.2%), anemia (31.8%), heart failure (10.1%), and malignancy (7.9%) **(Table 2)**. Vascular access was installed in the femoral vein in 57.9% of subjects, the jugular vein in 40.5% of subjects, and the subclavian vein in only 1.6% of subjects. Evaluation of ferritin, procalcitonin (PCT), and lactate levels was only performed in patients with infection, so they were not used as comparisons. Ferritin levels <1000 ug/L were found in 108 infected subjects, and procalcitonin levels >1.5 were found in 24 infected subjects. In addition, lactate levels >2 were found in 102 infected subjects.

Culture examinations were not performed on 130 subjects. Of the 188 subjects who had undergone culture examination, 61 samples did not show any bacterial growth, which could be due to the improper sampling technique and the timing of sampling, which could only be done after the subjects had received antibiotics. Furthermore, the most widely used antibiotics to treat transient vascular access infections were cefixime (53.2%), meropenem (10.6%), cefepime (6.4%), levofloxacin (6.4%), and ceftriaxone (6.4%). Based on the bivariate analysis, age was

Table 2. Clinical characteristics of research subjects.

Variables	Total
Age (years), Median (IQR)	
Age, n (%)	
≥ 60 years	101 (31.8)
< 60 years	217 (68.2)
Gender, n (%)	
Male	160 (50.3)
Female	158 (49.7)
Hemoglobin level, n (%)	
< 10 g/dL	101 (31.8)
≥ 10 g/dL	217 (68.2)
Albumin, n (%)	
Hypoalbuminemia (< 3.50 mg/dL)	193 (64.8)
Normoalbuminemia (≥ 3.50 mg/dL)	105 (35.2)
Random plasma glucose, n (%)	
DM (≥ 200 mg/dL)	206 (64.8)
Non-DM (< 200 mg/dL)	112 (35.2)
Duration of catheter use, n (%)	
≥ 30 days	21 (6.6)
< 30 days	295 (93.4)
Hypertension, n (%)	
Yes	204 (64.2)
No	114 (35.8)
Heart failure, n (%)	
Yes	32 (10.1)
No	286 (89.9)
Malignancy, n (%)	
Yes	25 (7.9)
No	292 (92.1)
Location of catheter use, n (%)	
Femoral vein	183 (57.9)
Jugular vein	128 (40.5)
Subclavian vein	5 (1.6)
Urea, Median (IQR)	162.5 (111.63-213)
Creatininea, Median (IQR)	7.89 (5.56-10.9)
Blood culture	
No bacterial growth was found	61 (31.9)
Not done	130 (68.1)

not a risk factor for infection (RR 0.938, 95%CI 0.696-1.266, p=0.675) **(Table 3)**.

DISCUSSION

Despite the benefits of providing adequate hemodialysis for patients initiating dialysis or awaiting permanent access, temporary vascular access has a higher risk of infection. Temporary vascular access infection is the second leading cause of mortality after cardiovascular events.[3] The incidence of catheter-related bloodstream infection ranges between 0.6 and 6.5 episodes per 1000 catheter days.[4] The pathogens use two main routes to reach the bloodstream: the extraluminal and intraluminal pathways. Regardless of the route used, after entering the bloodstream, the organisms can attach directly to the surface of the vascular access or become incorporated in the fibrin sheath that envelops the catheter and usually forms within 24 hours of catheter insertion. Adherence of organisms to the surface of the catheter initiates the formation of biofilms that are highly resistant to antibiotics. Therefore, it is clear that the most critical step in the treatment of catheter-related bloodstream infection (CRBSI) is preventing the attachment of microorganisms to the catheter and the formation of a biofilm. The first preventive step is to identify risk factors for infection, including gender, anemia, diabetes mellitus, duration of catheter use, old age, ferritin, hypoalbuminemia, and catheter insertion location.[4,5]

Several studies have shown that men have higher risks than women for developing catheter-related infections. Borges PRR et al showed that 65% of subjects with infection were males.[6] This was different from the results obtained from our study, where females had more infections (57.6%; OR 1.731; 95%CI 1.050-2.854; p=0.032) **(Table 4)**. This could happen since most of the female subjects in our study had more comorbidities and worse general condition when they first initiated hemodialysis.

Anemia is common in patients with chronic renal failure due to the shortened life span of red blood cells caused by hemolysis, folic acid deficiency, and bone marrow suppression by excess uremic substances, which further

Table 3. The comparison between independent variables with the proportion of temporary vascular access infection.

Variables	Infection		RR (95% CI)	p
	Yes	No		
Age, n (%)				
≥ 60 years	38 (37.6)	63 (62.4)	0.938 (0.696-1.266)	0.675
< 60 years	87 (40.1)	130 (59.9)		
Gender, n (%)				
Female	72 (45.6)	86 (54.4)	1.376 (1.041-1.817)	**0.023**
Male	53 (33.1)	107 (66.9)		
Anemia, n (%)				
Yes	53 (52.5)	48 (47.5)	1.582 (1.214-2.061)	**0.001**
No	72 (33.2)	145 (66.8)		
Hypoalbuminemia, n (%)				
Yes	87 (45.1)	106 (54.9)	1.246 (0.925-1.678)	0.138
No	38 (36.2)	67 (63.8)		
Diabetes Mellitus, n (%)				
Yes	95 (46.1)	111 (53.9)	1.722 (1.226-2.419)	**0.001**
No	30 (26.8)	82 (73.2)		
Duration of catheter use, n (%)				
≥ 30 days	15 (71.4)	6 (28.6)	1.951 (1.432-2.358)	**0.002**
< 30 days	108 (36.6)	187 (63.4)		
Location of catheter use, n (%)				
Femoral vein	72 (39.3)	111 (60.7)	4.728 (0.331-67.589)	0.252
Jugular vein	53 (41.4)	75 (58.6)	4.977 (0.347-71.274)	0.257
Subclavian vein	0 (0,.0)	5 (100.0)	Comparator	

Table 4. Multivariate analysis

Variables	OR (95% CI)	p
Gender: female	1.731 (1.050-2.854)	0.032
Anemia	2.293 (1.353-3.885)	0.002
Diabetes mellitus	2.962 (1.704-5.149)	<0.001
Duration of catheter use ≥ 30 days	5.322 (1.871-15.135)	0.002

causes failure of erythropoietin production and decreased red blood cell production. Additionally, iron deficiency is known to play a role in causing anemia in chronic renal failure patients. Iron is an essential element in the immune process. Iron deficiency can cause impaired phagocyte function and increase the risk of infection and death from infection.[7] Based on the results of a study by Wang K et al. involving 865 subjects, low hemoglobin levels were a significant risk factor for the incidence of infection (OR 2,276; 95%CI 1,0101-4,749; p=0.012) [8]. These results support the findings in our study where infection occurred in 52.5% of subjects who had anemia and 33.2% in subjects who did not have anemia (OR 2.293; 95%CI 1.353-3.885; p=0.002).

Diabetes causes immune system disorders, including decreased humoral and cellular immunity, which play a role in the pathogenesis of CRBSI. Diabetes causes decreased mobility of polymorphonuclear cells, chemotactic and phagocytic functions, and impaired adherence function, also decreased the number of T lymphocytes, especially CD4, which decreases the CD4:CD8 ratio. Grothe et al showed that diabetic patients in hypertonic conditions had a 22% greater chance of catheter infections. Menegueti et al reported the result of a case-control study indicating that diabetes mellitus was a risk factor for catheter infection (OR 2.651; p<0.001). Another study by Sahli et al. also proved that diabetes significantly increases a person's risk of CRBSI.[4,8,9] Similarly, a retrospective cohort study by Çaylan R et al. found that diabetes mellitus was associated with infection (OR 2.20; 95%CI 1-4.82; p=0.049).[10] This was in line with the results obtained from this study; 76% of the infected subjects were diabetic (OR 2.962; 95%CI 1.704-5.149; p<0.001).

Generally, the recommended duration of catheter use is <21 days, but the 30-day limit was used in this study.[11] Napalkov et al. reported that most temporary vascular access infections occurred within the first 90 days, with an incidence rate of 5.1 per 1000 catheter days. The risk of infection was also higher as the duration of use increased, going up to 3.3 times in a period >90 days.[8] Meanwhile, Borges PRR et al. found that an average catheter infection occurred after 9 days of use.[6] These results were supported by Oliver MJ et al.[12] through his research which showed the possibility of bacteremia on the first day of catheter insertion was 1.9% and significantly increased to 13.4% on the second day. This indicated an association between the increased risk of CRBSI and the duration of catheter use. Similar results were obtained from our study, where there were 71.4% of subjects using catheters >30 days developing an infection (OR 5.322; 95%CI 1.871-15.135; p<0.002), compared to 63.4% of patients using catheter <30 days who did not have an infection.

There are changes in non-specific systems that happen due to aging that facilitates the invasion of pathogenic organisms into the mucosal tissue. Increase in the plasma concentration of IL-6, IL-1, and tumor necrosis factor-alpha (TNF-α) in the elderly was also shown to be a predictor of functional disability and mortality and causes continuous stimulation of the immune system, resulting in a subclinical inflammatory state or what is known as inflamm-aging. The aging process also impacts the specific immune system, causing a decrease in the number of T and B lymphocytes.[13]

Our analysis showed no statistically significant correlation between age >60 years and infection. This could be because the mean age in all groups with temporary vascular access was 51.7 years, and 68.2% of the infectious subjects were aged <60 years old. Similar results were

found by the study of Borges PRR et al where age was not a significant risk factor for infection.[6]

Ferritin indicates the amount of iron stored in the body. A high ferritin level in the serum shows high iron content in the body. CKD patients undergoing dialysis therapy generally have iron overload caused by the body's increased need for red blood cells, so they need to be given iron intravenously, with or without red blood cell transfusions. Simultaneously, excess iron can cause damage to neutrophils and T cell function. Ferritin protects the body during infection by limiting the availability of iron used by pathogens for multiplication and colony formation.

A study by Seifert et al showed an increased incidence of bacterial infection in hemodialysis patients with ferritin levels ranging from 1001-2000 ng/mL compared to patients with serum ferritin levels ranging from 10-220 ng/mL ($p<0.01$).[7] Another prospective study reported a 2.92 times greater risk in patients undergoing hemodialysis with ferritin levels >1000 ng/mL than those with ferritin levels <1000 ng/mL.[14] The relationship between ferritin levels and the risk of infection in this study could not be analyzed further because a ferritin examination was not performed on every subject undergoing hemodialysis.

Hypoalbuminemia is common in patients undergoing dialysis. Inadequate nutrition is associated with impaired immunity, increasing the likelihood of becoming infected.[15] Lukowsky et al reported that one-third of deaths within the first 90 days in patients undergoing hemodialysis was associated with hypoalbuminemia. The multivariate analysis emphasized that albumin levels <33 g/dL were an independent predictor of catheter infection. A case-control study conducted by Adeniyi OA, et al.[16] found that serum albumin levels before treatment in subjects with vascular access infection were in the range of 2.4 ± 0.6 g/dL, while for the group of subjects who did not have an infection, had an albumin value of 3.2 ± 0.6 g/dL ($p<0.0001$). Another study by Darma et al also showed an increased risk of catheter-associated bacteremia in patients with hypoalbuminemia ($p<0.008$).[17,18] In addition, similar findings were also shown by Demirci et al,[3] where low albumin levels were an independent predictor of the occurrence of CRBSI (OR 0.119, 95% CI 0.019-0.756, $p=0.024$).[15] Our study was consistent with the results, where 69.6% of subjects with hypoalbuminemia had an infection, while only 30.4% of subjects were infected in the group with a normal albumin level.

The location of catheter insertion could also impact the incidence of infection. Insertion of temporary CVC to the femoral vein is associated with a higher risk of infection. Sahli et al reported that the incidence of infection in CVC installed in the femoral vein is 8.8 per 1000 catheter days. Meanwhile, the subclavian vein has the lowest risk of infection, despite a higher risk of stenosis. Thus, the internal jugular vein is preferred for hemodialysis.[4,19] This risk of stenosis was also the exact reason for not preferring the subclavian vein as a CVC insertion site at Cipto Mangunkusumo Hospital; hence the correlation between the catheter insertion location and the risk of infection in our study could not be analyzed further.

KDOQI recommended that health workers who come into contact with catheters must use clean or sterile masks and gloves. Liquids that can be used to clean the exit sites are 2% chlorhexidine and 70% alcohol or 10% povidone-iodine liquid. Several studies and meta-analyses have shown that chlorhexidine is superior to alcohol and povidone-iodine. Technical implementation of exit-site maintenance at Cipto Mangunkusumo Hospital has also used 2% chlorhexidine.[5]

The use of topical antibiotics at the exit site has been associated with a 75-93% reduced risk of CVC-associated bacteremia. One of the recommended topical antibiotics, which are used in Cipto Mangunkusumo Hospital, is mupirocin. In addition, antimicrobial lock prophylaxis has been shown to reduce the risk of CVC-related bacteremia. Antimicrobial lock combination prophylaxis, which is currently being used at Cipto Mangunkusumo Hospital, is gentamicin 40 mg and heparin 2000 units. This use was in line with the International Society of Nephrology recommendations: gentamicin 5 mg/ml + heparin 5000 U/mL. Overall, this could

cause a low incidence of CVC infection in Cipto Mangunkusumo Hospital.[5]

Our study has several limitations. First, this study was a retrospective study that relied on medical record data; thus, it may not fully reflect the patient's condition if there were improper or incomplete documentation in the medical record. Second, data collection was only done in one hospital; therefore, the results obtained may not represent the results from other hospitals. Third, we did not assess the comorbid factors of each subject before temporary vascular access insertion, which could inherently affect the patient's susceptibility to infection.

CONCLUSION

The proportion of temporary vascular access infections at the Cipto Mangunkusumo Hospital was 39.3%. The significant risk factors for temporary vascular access infection were female gender, diabetes mellitus, low hemoglobin level, and the duration of catheter use >30 days. We recommend that ferritin examination be performed routinely in all patients with temporary vascular access, regardless of the infection status. Blood cultures should be examined twice, with samples from peripheral veins and hemodialysis catheters taken before administration of antimicrobial therapy and observed for 48 hours of incubation. Culture studies should be performed after excluding other possible infection causes in patients with fever. More research should be carried out, preferably using a prospective design, to assess the actual condition of the patient better and to be able to follow the patient's course of disease continuously. Lastly, further research should pay more attention to the characteristics and proportions of each of the subjects involved to show more accurate results and reduce the possibility of bias.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Kresna Dharma Suryana. The first draft of the manuscript was written by Kresna Dharma Suryana, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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