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Assessing Hemodialysis Access Failure Risk in Subjects Based on COVID-19 Status

COVID-19 Durumuna Göre Hemodiyaliz Erişim Sorunu Riskinin Değerlendirilmesi

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ÖZ

Amaç: COVID-19 nedeniyle yoğun bakıma kabul edilen hastalarda %30'a varan oranda trombotik komplikasyonlar bildirilmiştir. Bununla birlikte, COVID-19'lu kişilerde hemodiyaliz erişim sorununa ilişkin veriler sınırlıdır. Bu çalışma, özellikle COVID-19 durumu açısından hemodiyaliz erişim sorunu sıklığını ve belirleyicilerini araştırmayı amaçlamıştır.
Araçlar ve yöntem: Bu çok merkezli kesitsel çalışma, kalıcı hemodiyalize giren kişiler arasında yürütüldü. Hastalar erişim sorunu olan ve olmayanlar olarak iki gruba ayrıldı. Çalışmanın birincil sonuç ölçütleri, iki grup arasındaki hasta özellikleri, laboratuvar ölçümleri ve COVID-19 pozitifliğindeki farklılıklardı. İkincil sonuç ölçüsü, hemodiyaliz erişim başarısızlığı ile bağımsız olarak ilişkili faktörlerin tanımlanması olarak tanımlandı.
Bulgular: 26 (%12.2) hastada hemodiyaliz erişim sorunu oluştu. Tip 2 diyabet (%76.9'a [n=20] karşı %50 [n=93], p=0.018), diyaliz sırasında hipotansiyon (%88.5'e [n=23] karşı %58.1 [n=108], p=0.006) ve COVID-19 pozitifliği (%73.1'e [n=19] karşı %15,1 [n=28], p<0.001) erişim sorunu olan hastalarda anlamlı olarak daha sıktı. Çok değişkenli lojistik regresyon, bu faktörlerin üçünün de bağımsız olarak daha yüksek hemodiyaliz erişimi başarısızlığı olasılığı ile ilişkili olduğunu gösterdi.
Sonuç: Hemodiyaliz erişim sorunu, COVID-19'lu kişilerde COVID-19 olmayanlara göre daha sık görülmektedir.

Anahtar Kelimeler: böbrek; diyaliz; koronavirüs; tıkanma

ABSTRACT

Purpose: Thrombotic complications have been reported in up to 30% of patients admitted to the intensive care unit for COVID-19. However, data on hemodialysis access failure in patients with COVID-19 are limited. This study aimed to investigate the frequency of hemodialysis access failure and its determinants, especially with respect to COVID-19 status.
Materials and Methods: This multi-center cross-sectional study was conducted among subjects undergoing permanent hemodialysis. Patients were divided into two groups, those with and without access failure. The primary outcome measures of the study were differences in patient characteristics, laboratory measurements and COVID-19 positivity between the two groups. The secondary outcome measure was defined as the identification of factors independently associated with hemodialysis access failure.
Results: Hemodialysis access failure occurred in 26 (12.2%) patients. Type 2 diabetes (76.9% [n=20] vs. 50% [n=93], p=0.018), hypotension during dialysis (88.5 [n=23] vs. 58.1% [n=108], p=0.006) and COVID-19 positivity (73.1% [n=19] vs. 15.1% [n=28], p<0.001) were significantly more frequent among patients with access failure. Multivariable logistic regression showed that all three factors were independently associated with a higher likelihood of hemodialysis access failure.
Conclusion: Hemodialysis access failure is encountered more frequently in patients with COVID-19 compared to those without COVID-19.

Keywords: coronavirus; dialysis; kidney; occlusion

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INTRODUCTION

The number of patients with chronic kidney disease (CKD) is increasing worldwide, largely in correlation with the age and the prevalence of type 2 diabetes. About 10% of the general population is estimated to be affected by CKD.[1] Advances in medical care and access to hemodialysis have reduced mortality from CKD; however, the effect of the COVID-19 pandemic on hemodialysis use and its success requires investigation.

Subjects with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 are generally considered for initiation of hemodialysis.[2] Patients undergoing renal replacement therapy are scheduled for hemodialysis thrice weekly. Creation of a native primary arteriovenous fistula (AVF) is the access of choice due to favorable survival characteristics and low complication rates.[3] In patients who are not candidates for fistula creation due to poor vascular characteristics or advanced heart failure, catheters are used to maintain hemodialysis, and thus, the patency of hemodialysis access is critical for such patients.[4] Access failure may lead to insufficient hemodialysis and ultrafiltration which can promote life-threatening complications.[5] However, both AVFs and catheters are prone to failure due to various causes. Thrombosis is the leading cause of access failure, accounting for 65–85% of cases in which permanent access loss occurs.[6]

COVID-19 is a systemic disease that primarily affect the lungs and is closely associated with various impacts on other systems,[7,8] including the hematopoietic system and coagulation systems. In fact, thrombotic complications have been reported in up to 30% of patients admitted to the intensive care units (ICU) for COVID-19.[9] Thrombosis of intravenous catheters or extracorporeal circuits and arterial vascular occlusive events have also been reported in subjects with COVID-19.[10] However, data concerning hemodialysis access failure in subjects with COVID-19 are limited.

This study aimed to investigate the frequency of hemodialysis access failure and its determinants during the COVID-19 pandemic, including patients from five centers.

MATERIALS and METHODS

This multi-center cross-sectional study was conducted among subjects undergoing permanent hemodialysis at Kırşehir Training and Research Hospital, Kaman State Hospital, Mucur State Hospital, Kozanoğlu Hemodialysis Center, and Kırşehir Hemodialysis Center between March 2020 and March 2022. All subjects provided written informed consent. The study was approved by Ahi Evran University Ethics Committee (approval number: 2021-04/41) and was conducted in accordance with the tenets of Helsinki Declaration.

Demographic data including age, sex, comorbid diseases, current anticoagulant and antiaggregant medication use, anticoagulation during hemodialysis, duration of hemodialysis, type of access and access site, duration of the access, presence of hypotension during hemodialysis, presence of recent hospitalization, and laboratory test results, COVID-19 PCR (Polymerase Chain Reaction) test results were recorded for all subjects. Hypotension during hemodialysis was defined as a recurrent drop in systolic blood pressure below 90 mmHg or at least 20 mmHg with accompanying clinical symptoms.[11] Subjects were divided into two groups according to the presence or absence of access failure: Group 1 included subjects without access failure (n=186) and Group 2 included subjects with hemodialysis access failure (n=26).

The primary outcome measure of the study was to determine the differences in demographic and clinical characteristics, laboratory measurements and COVID-19 PCR test positivity between subjects with and without hemodialysis access failure. The secondary outcome measure was to identify factors independently associated with hemodialysis access failure.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), with a 5% alpha error probability to determine significance. For the normality check, the histogram and Q-Q plots were used. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to the normality of distribution and as

frequency (percentage) for categorical variables. Continuous variables were analyzed with the Student's *t*-test or Mann-Whitney U test, depending on the normality of distribution. Categorical variables were analyzed using chi-square tests or Fisher's exact tests. Multivariable logistic regression analysis (forward conditional method) was performed to determine factors independently associated with hemodialysis access failure. Nagerkerke R2 was given to represent explained variability in the dependent variable by the logistic regression model. Stacked bar chart was used to describe the data as a figure.

RESULTS

A total of 212 patients (mean age 64.70±14.15 years, 62.3% male) undergoing permanent hemodialysis were included in the study. Hemodialysis access failure occurred in 26 (12.2%) patients. Subjects with and without hemodialysis access failure were similar with respect to age, sex, and the presence of hypertension, hyperlipidemia, previous cerebrovascular event, malignancy, coronary artery disease, heart failure, and chronic obstructive pulmonary disease. However, type 2 diabetes was more frequent in subjects with hemodialysis access failure compared to those without access failure (76.9% vs. 50%, p=0.018).

The two groups were similar with regard to the use of aspirin, clopidogrel, warfarin and low-molecular-weight heparin. 80.2% of the study population received weight adjusted unfractionated heparin and 14.6 % of the study population received low-molecular weight heparin during hemodialysis. The median duration of hemodialysis was 34 (14.5-76) months. The median duration of hemodialysis was significantly shorter in subjects with hemodialysis access failure compared to those without hemodialysis access failure (18.5 [10-46] months vs. 36.5 [16-80] months, p=0.026).

AVF was used for hemodialysis in 66.5% of the study population and the remaining 33.5% of the subjects underwent hemodialysis through catheters. In subjects with hemodialysis access failure, the use of catheters instead of AVF was more frequent compared to those without hemodialysis access failure (69.2% vs. 28.5%, p<0.001). The median duration of hemodialysis was 25.5 (13-49) months. Reported hypotension was more frequent among subjects with hemodialysis access failure compared to those without hemodialysis access failure (88.5 vs. 58.1%, p=0.006). PCR test positivity for COVID-19 was also more frequent in subjects with hemodialysis access failure compared to those without hemodialysis access failure (73.1% vs. 15.1%, p<0.001) (Figure 1). Leukocyte count (3.90 [3.48-5.32] x 10^3 vs. 5.59 [3.86-7.30] x 10^3, p=0.004), neutrophil count 2.56 [2.19-2.97] x 10^3 vs. 3.30 [2.37-4.88] x 10^3, p=0.002), and lymphocyte count 0.74 [0.44-1.01] x 10^3 vs. 1.17 [0.80-1.61] x 10^3, p<0.001) were significantly lower among subjects with hemodialysis access failure compared to those without hemodialysis access failure (Supplement Table 1).

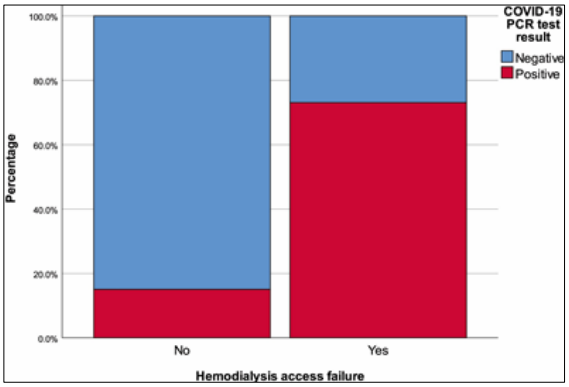

Figure 1. COVID-19 PCR test results with regard to hemodialysis access failure (chi-square = 41.209, p<0.001).

Multivariable logistic regression analysis had revealed that, patients with diabetes mellitus had 4.506-fold higher risk for access failure than other patients had (OR: 4.506, 95% CI: 1.344 - 15.111, p=0.015). Patients with a catheter had a 4.031-fold higher risk of access failure than patients with an arteriovenous fistula had (OR: 4.031, 95% CI: 1.334- 12.181, p=0.013). Patients who had hypotension attacks during hemodialysis had a 4.003-fold higher risk for access failure than other patients (OR: 4.003, 95% CI: 1.016-15.773, p=0.047). COVID-19 positive patients had a 12.458-fold higher risk for access failure than COVID-19 negative patients had (OR: 12.458, 95% CI: 3.910-39.690, p<0.001). In addition, low lymphocyte count was independently associated with the access failure (p=0.017) (Table 2). Other variables included in the analysis, age (p=0.618), sex (p=0.566), duration of dialysis (p=0.241), white blood cell count (p=0.451), neutrophil count (p=0.189), lymphocyte percentage (p=0.820), hospitalization (p=0.144) were found to be insignificant. Nagelkerke

R2 was 0.522 so logistic regression model has good performance to explain hemodialysis access failure.

Table 2. Significant factors independently associated with the hemodialysis access failure, multivariable logistic regression analysis.

	β coefficient	Standard error	p	Exp(β)	95.0% CI for Exp(β)	
Diabetes mellitus	1.505	0.617	0.015	4.506	1.344	15.111
Type of access, Catheter	1.394	0.564	0.013	4.031	1.334	12.181
Hypotension during hemodialysis	1.387	0.700	0.047	4.003	1.016	15.773
COVID-19 PCR test positivity	2.522	0.591	<0.001	12.458	3.910	39.690
Lymphocyte (x103)	-1.294	0.541	0.017	0.274	0.095	0.791
Constant	-4.327	0.939	<0.001	0.013		

CI: Confidence Interval, Nagelkerke R2=0.522

DISCUSSION

This study shows that subjects with hemodialysis access failure are more likely to be diabetic, to have catheters for hemodialysis, more often experience hypotension during hemodialysis, and more frequently have positive COVID-19 PCR test. The duration of hemodialysis is shorter in subjects with hemodialysis access failure compared to those without failure. Subjects who have diabetes, those undergoing hemodialysis with a catheter, and those with hypotension during hemodialysis have considerably elevated risk for access failure. Moreover, subjects with a positive COVID-19 test have a 12-fold increased risk of hemodialysis access failure.

Patency of the access site is critical for subjects undergoing hemodialysis. Several factors have been shown to be associated with hemodialysis access failure.[4] The leading cause of hemodialysis access failure in subjects with an AVF is thrombosis, accounting for 65–85% of such cases. Thrombosis also constitutes the most frequent cause of malfunction in subjects undergoing hemodialysis through catheters.[6]

Diabetes has been shown to be a frequent cause of access failure both in subjects with AVFs and catheters. Subjects without diabetes have 60% lower risk of catheter malfunction compared to those with diabetes.[12] A recent meta-analysis of 23 studies, including 930 diabetic and 3137 non-diabetic patients undergoing hemodialysis through an AVF, have reported an increased rate of hemodialysis access failure in diabetic subjects compared to non-diabetics.[13] Consistent with previous data, our findings demonstrated an increased risk of hemodialysis access failure in a pooled population of subjects with catheters and AVFs.

COVID-19 patients have been reported to be at an increased risk for venous thromboembolism, which is also a feature of various diseases in which uncontrolled inflammation is observed.[14,15] Thromboembolism occurs in up to 1/3 of COVID-19 patients.[16] The combined impact of systemic inflammation, abnormal coagulation, and multiorgan dysfunction is believed to promote thrombosis through oxidative stress and other mechanisms,[15] which has been demonstrated particularly in subjects with COVID-19.[17] Elevated fibrinogen and D-dimer levels in subjects with COVID-19 are indicators for the risk of thromboembolic events.[18] COVID-19 associated coagulopathy is characterized by mild thrombocytopenia, mildly prolonged prothrombin time, increased fibrinogen and raised D-dimer (resembling sepsis-induced coagulopathy) and disseminated intravascular coagulation.[19] Direct invasion of endothelial cells by SARS-CoV-2 or the inflammatory process promoted by COVID-19 damages the endothelium. This condition has been demonstrated to result in a self-sustaining vicious cycle of endothelial injury,[20] which has been suggested to trigger microthrombosis in patients with COVID-19.[21] Disruption of intercellular junctions during COVID-19 in conjunction with endothelial dysfunction exposes subendothelial tissue factor and collagen, further activating coagulation.[22] Moreover, fibrinolysis is also reduced in subjects infected by SARS-CoV-2, particularly through the release of plasminogen activator inhibitor-1, which inhibits conversion of plasminogen to plasmin.[23]

The consequences of increased thrombosis in COVID-19 have been reported in distinct patient subsets. The risks for venous thromboembolism, thromboembolic stroke, myocardial infarction, peripheral arterial embolism, and pulmonary embolism are increased in subjects with COVID-

19.[24-28] Moreover, limited data indicate that hemodialysis access may be complicated by COVID-19.[29,30] Our findings clearly indicate that hemodialysis access failure is encountered more commonly among subjects with COVID-19 compared to those without COVID-19. Moreover, COVID-19 infection appears to lead to an extreme increase in the likelihood for hemodialysis access failure. Given recent findings of increased thrombosis in subjects with COVID-19, intensifying anticoagulant management in subjects undergoing hemodialysis should be considered.

This study has some limitations to be mentioned. The limited sample size and low number of patients with hemodialysis access failure is a drawback to be noted. Moreover, the cross-sectional design of the study limits generalization of our results to all COVID-19 patients undergoing hemodialysis. Nevertheless, we believe that this study provides insight into the risk of hemodialysis access failure in the COVID-19 era, which is critical in subjects with CKD.

In conclusion, hemodialysis access failure is more frequently encountered among subjects with COVID-19 compared to those without COVID-19. Although other factors, such as diabetes and hypotension, also increase failure risk, the presence of COVID-19 leads to a 12-fold increase in the likelihood for hemodialysis access failure. It is essential to provide meticulous management of anticoagulation in this particular patient subset.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

The study was approved by the Ahi Evran University Ethics Committee (approval number: 2021-04/41) and was conducted in accordance with the Helsinki Declaration.

Authors' Contributions

Concept/Design: AB, AG, BB. Data Collection and/or Processing: AB, AG, BB. Data analysis and interpretation: AB, AG, BB. Literature Search: AB, AG, BB. Drafting manuscript: AB, AG, BB.

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