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Clinical and epidemiological analysis of COVID-19 in End-Stage Renal Disease patients undergoing maintenance hemodialysis: A study from Golestan province

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Abstract

Background: End-Stage Renal Disease (ESRD) patients under maintenance hemodialysis are at higher risk for COVID-19 and severe outcomes. This study aimed to investigate the association between ESRD patients who underwent maintenance hemodialysis at 5th Azar and Sayad Shirazi Hospital in Golestan Province in 2019 and their risk of acquiring and experiencing severe outcomes from COVID-19. Furthermore, this study aimed to provide insights into the epidemic status of COVID-19 in this specific population, contributing to better insight into the unique challenges faced by ESRD patients on hemodialysis during the pandemic.

Methods: This retrospective descriptive cross-sectional study was performed on patients who underwent maintenance hemodialysis. The diagnosis was made based on diagnostic criteria and COVID-19 PCR test. Medical information of all participants was collected. Medical information including clinical, laboratory, and radiological data as well as morbidity and mortality were collected and analyzed by experts. Statistical analysis was performed using SPSS version 21. Normality was evaluated using Shapiro-Wilk test and comparison between groups was analyzed using student T-test and Mann-Whitney U tests (P-Value < 0.05).

Results: The most prevalent radiological findings were ground glass opacities, observed in 46.7% of cases, followed by linear opacities, noted in 26.7% of cases. Most patients (86.6%) were discharged and four of them (13.4%) passed away. WBC, serum creatinine, and age were significantly associated with ESRD patients' mortality (P-Value < 0.05). The patients who passed away were old and had higher levels of WBC and creatinine (P-Value > 0.05). No significant difference was observed between the age and BMI of passed away and discharged patients. None of the other laboratory parameters in the two groups of passed away and discharged patients with COVID-19 showed a significant difference (P-Value > 0.05).

Conclusion: ESRD patients who underwent hemodialysis due to their underlying problems and the crowded environment of dialysis wards more than the general population are at risk of getting COVID-19.

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Highlights

What is current knowledge?

- COVID-19 disease has a severe effect on ESRD patients that is receiving chronic hemodialysis.
- In hemodialysis patients, several other diseases such as diabetes and hypertension are associated with poor outcomes due to COVID-19.

What is new here?

- Elevated WBC and creatinine levels are vital determinants of death among ESRD patients diagnosed with COVID-19.
- No association was found between CRP levels and duration of kidney dialysis in patients with COVID-19.

Introduction

The World Health Organization (WHO) officially declared COVID-19 a global pandemic in mid-June 2020 (1). Symptoms associated with COVID-19 are nonspecific, including fever (44-98% of patients), dry cough (68-76% of patients), and muscle pain (Observed in 18% of patients). Mortality rates vary, ranging from 2.3% in China to 7.2% in Italy (2,3).

In individuals affected by COVID-19, particular consideration should be given to certain demographic groups. Epidemiological investigations indicate that individuals with diabetes, hypertension, cardiovascular diseases, or those in the elderly demographic face an elevated susceptibility to contracting COVID-19, with a heightened likelihood of experiencing severe manifestations and requiring specialized care or succumbing to the disease (4,5). Patients undergoing maintenance dialysis are prone to an elevated risk of contracting COVID-19 and experiencing its complications (3). Epidemiological studies indicate that the kidney is an important target of COVID-19 (6). Acute kidney injury (AKI) occurs in 5-15% of cases, and the presence of COVID-19 is identified as an independent risk factor for mortality (7). Patients with Chronic Kidney Disease (CKD), those undergoing chronic replacement therapy, and kidney transplant recipients are also affected by COVID-19. Hemodialysis patients may have a higher risk of contracting COVID-19 because of possible cross-contamination in confined spaces and issues with both their adaptive and innate immune systems. Furthermore, the hemodialysis patient population exhibits a higher prevalence of severe comorbidities such as cardiovascular disease, hypertension, and diabetes mellitus, all of which are linked to an elevated risk of adverse outcomes. This review is centered on exploring the clinical aspects of COVID-19 in hemodialysis patients (8).

After the binding of the SARS-CoV-2 antigen protein to angiotensin-converting enzyme 2 (ACE2) receptors, the S protein undergoes cleavage and activation by the serum family of membrane proteases (TMPRSS). This activation enables the virus to cleave the fusion peptide, facilitating its release (9). Acute kidney failure in COVID-19 may result from a synergistic effect involving both the direct cytotoxic impact of the virus and the systemic inflammatory response triggered by cytokines. This form of renal failure is particularly evident in critically ill patients, those with acute respiratory distress syndrome (ARDS), and individuals requiring intensive care unit (ICU) admission. Additional potential mechanisms contributing to acute renal failure include acute tubular necrosis (ATN) due to multiple organ failure and shock, as well as a potential pre-renal cause stemming from volume depletion associated with reduced oral intake and high fever. Factors such as drug toxicity, hemodynamic involvement, and exposure to contrast material also have the potential to play a role in this context (10).

Evaluation for acute kidney failure in COVID-19 should follow the same protocols used for other causes of acute kidney failure. Several factors can contribute to acute renal failure, including acute ischemic tubular injury, nephrotoxic acute tubular injury, or a combination of both, acute interstitial nephritis, glomerular disease, prerenal azotemia, and unspecified causes. Some factors involved in these various conditions may include hypotension, shock, atrial fibrillation, prolonged volume depletion, rhabdomyolysis, exposure to toxic agents such as vancomycin and iodinated contrast, as well as evident proteinuria (11). Additionally, the degree and severity of lung involvement can be evaluated with CT intensity score. This quantification plays an important role in modifying the treatment plan in some cases in critical patients with COVID-19. The CT severity score reveals the actual lung involvement percentage due to the COVID-19. Briefly, CT severity score ≤ 8 indicates mild disease, CT severity score between 9 -15 means moderate disease, and CT severity score >15 reveals severe disease (12). Further, hemodialysis patients may be susceptible to COVID-19 and

its systemic consequences due to the following reasons: 1. increased risk of transmission, 2. chronic immune system dysfunction, 3. endothelial dysfunction, 4. organ damage with reduced structural or functional reserve, and 5. prior comorbidity and increased risk of renal system dysfunction due to reduced structural organ reserve (3,10).

The effect of the COVID-19 epidemic on chronic kidney disease and end-stage kidney patients has not yet been fully determined. Considering the low immune function of uremic patients, the situation of the epidemic of COVID-19 in these patients should not be ignored. In this study, we intend to describe the frequency of COVID-19 and its characteristics in the main hemodialysis centers of the Golestan Province. In this study, the epidemiological, clinical, laboratory, and radiological characteristics of these patients are investigated, and we expect that our findings will contribute to the proper management of this disease in dialysis units.

Methods

This descriptive cross-sectional study was conducted on patients undergoing maintenance hemodialysis with positive RT-PCR (Real-Time PCR) and chest CT (Computed Tomography) scan graph for COVID-19 in the hemodialysis department of 5 Azar and Sayad Shirazi Hospital in Golestan Province in 2019. After obtaining the relevant ethical permits from the academic authorities and coordinating with the officials of 5 Azar and Sayyad Shirazi Hospital to access and use the information of hospitalization records of the dialysis patients infected with COVID-19 in those centers, the required information was obtained through the patients' files.

Demographic information of patients (Age, gender, ethnicity), clinical symptoms of patients (Fever, myalgia, shortness of breath, dry cough, anorexia, weakness, and lethargy, decreased level of consciousness) and laboratory tests ((Calcium, phosphorus), sodium, potassium, CBC (Complete Blood Count), AlP (Alkaline Phosphatase), TG (Triglycerides), Chol (Cholesterol), AST (Aspartate Transferase), ALT (Alanine Transferase), Alb (Albumin), Ferritin, CRP (C-Reactive Protein) and ESR (Erythrocyte Sedimentation Rate)), patient dialysis variables (Dialysis adequacy (KT/V), time per session in hours, number of sessions per week) and The radiological data (CT scan of the chest) were recorded by the operator in the Registration form. Dialysis adequacy usually refers to how well toxins and waste products are removed from the patient's blood, which has a major impact on their well-being. Moreover, Kt/V is a metric used to assess the effectiveness of a hemodialysis session.

Also, additionally, information regarding the underlying diseases of the patients was collected. During the follow-up period, the cases of death of these patients were recorded, and the possible cause of death was suggested by the research team, based on its time, place and, clinical manifestations.

Research limitations

Access to a sufficient and appropriate number of patient samples was one of the study's limitations. Another limitation of this study is the lack of follow-up on discharged patients and the lack of measuring their mortality rates over the medium to long term. Besides, due to the high cost of inflammatory markers kits, we could not examine all of these markers in all of the patients.

Ethical consideration

This study, conducted on hemodialysis patients with COVID-19, prioritized ethical standards. Necessary permits were obtained, and collaboration with hospital officials ensured confidential use of patients' records. Patient confidentiality was strictly maintained, and informed consent was obtained when applicable. Transparency and communication were upheld to safeguard participant welfare and research integrity. The study adhered to ethical guidelines in all stages, respecting patient rights and promoting data security.

Statistical analysis

All results were analyzed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). To determine the normality, we performed the Shapiro-Wilk test. For data analysis, we used the student T-test or Mann-Whitney U test according to the normality results. Moreover, $p < 0.05$ was considered to indicate a statistically significant difference. In addition, we considered the conditions of the Chi-square test such as Random Sampling, as well each observation is related to one person, and no person is counted twice in the sampling.

Results

Demographic frequency of hemodialysis patients with COVID-19

Out of 198 hemodialysis patients, 30 qualified for this study. Thirty-five patients were excluded because they had missing or negative PCR results, did not require hospitalization, or had passed away. The mean age of the cohort was 58.97 ± 11.88 years (Range 34-83). Of these, 16 (53.3%) were female and 14 (46.7%) males The majority of the patients identified as Persian (26 patients, 86.7%), with smaller numbers representing Turkman (1 patient, 3.3%), Sistani (2 patients, 6.7%), and Cossack (1 patient, 3.3%) ethnicities. The distribution of body mass index (BMI) showed that 17 patients (56.6%) had a BMI within the 18.5-24.9 range, seven patients (23.3%) were considered overweight with a BMI of 25-29.9, and six patients (20%) were classified as obese with a BMI of 30-34.9. None of the patients had a BMI below 18.5 or 35 or above.

Proportion of underlying disease history with COVID-19

This study analyzed the medical records of hemodialysis patients with COVID-19 and found that hypertension was the most common comorbidity, affecting 24 patients (76.7%), followed by diabetes, which was present in 15 patients (50%). Coronary heart disease was observed in 3 patients (10%), and one patient (3.3%) had a history of kidney transplantation. The initial clinical symptoms primarily consisted of fever (80%), dyspnea (83.3%), weakness and lethargy (63.3%), and anorexia (33.3%). Notably, cough and myalgia were reported in 10% and 33.3% of patients, respectively. COVID-19 diagnosis was confirmed through PCR testing. Radiological evaluation showed ground-glass opacities in 46.7% of cases, linear opacities in 26.7%, and bilateral consolidation in 16.7%, with multilobar involvement noted in 10% of patients. In the short term, 26 patients (86.6%) were discharged, and 4 patients (13.4%) passed away during the study period.

Laboratory findings in hemodialysis patients with COVID-19

Mann-Whitney U tests revealed that age, white blood cell (WBC) count, and serum creatinine levels were significant predictors of mortality ($p < 0.05$), with deceased patients being older and having higher values in these parameters. No significant difference in body mass index (BMI) was found between survivors and non-survivors. The Kolmogorov-Smirnov test confirmed the normality of other laboratory variables, including triglycerides, cholesterol, platelets, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), ferritin, calcium, potassium, and phosphorus ($p > 0.05$), allowing for comparison using Student's t-test. As shown in Table 1, none of these variables differed significantly between the two groups ($p > 0.05$), except for age ($p = 0.02$), WBC count ($p = 0.037$), and creatinine ($p = 0.033$).

Table 1. Mean and standard deviation of laboratory and demographic variables in hemodialysis patients with COVID-19

Parameters	Groups		P-value
	Recovered patients	Expired patents	
Age*	49.5±12.28	62±9.69	0.02
BMI*	25.41±2.82	28.67±6.18	0.560
WBC count*	6.85±3.87 ×10 ^{3}/µL	11.55±4.57 ×10 ^{3}/µL	0.037
Hb*	10.49±2.22×10 ^{6}/µL	9.00±1.52×10 ^{6}/µL	0.096
ALT*	35.55±28.34 IU/L	31.42±6.02 IU/L	0.188
ALP*	293.43±127.72 U/L	437.42±389.91 U/L	0.872
Alb*	3.61±0.78 gr/dl	3.34±0.69 gr/dl	0.229
ESR*	49.52±22.80 mm/hr	61.42±29.10 mm/hr	0.561
CRP*	10.76±14.65	2.65±1.18	0.288
Cr*	5.17±0.84 mg/dl	6.65±2.17 mg/dl	0.033
Na*	142.56±14.19 mEq/dl	136.57±2.57 mEq/dl	0.146
TG**	154.34±78.87 mg/dl	140.85±28.72 mg/dl	0.390
Chol**	173.04±61.22 mg/dl	180.28±42.17 mg/dl	0.671
BUN**	123.86±38.45 mg/dl	99.14±36.23 mg/dl	0.634
PLT**	265.86±94.21×10 ^{3}/µL	163.42±103.64 ×10 ^{3}/µL	0.080
LDH**	410.13±79.93 mg/dl	408.00±77.43 mg/dl	0.947
Ferritin**	329.82±168.64 ng/ml	295.71±145.82 ng/ml	0.928
Ca**	8.52±0.83 mg/dl	7.98±0.54 mg/dl	0.080
P**	4.93±1.29 mEq/dl	5.55±1.18 mEq/dl	0.211
K**	4.96±0.89 mEq/dl	4.64±1.12 mEq/dl	0.392

* Means Mann-Whitney U test and ** Means Student T-test.

Association of comorbidities with mortality of hemodialysis patients with COVID-19

Exact fisher test analysis indicated that COVID-19 patients with a history of diabetes had significantly higher mortality rates (P-Value < 0.05). However, no significant associations were found between mortality and conditions such as coronary heart disease, polycystic kidney disease, or prior kidney transplantation (P-Value > 0.05). As summarized in Table 2, these results emphasize diabetes as critical comorbidities associated with increased mortality in this group.

Table 2. Frequency and percentage of the underlying disease of hemodialysis patients with COVID-19 based on the patient's outcome

Underlying disease	Yes/No	Recovered patients	Expired patients	P-value
T2DM*	No	14 (93.3%)	1 (6.7%)	0.040
	Yes	9 (60%)	6 (40%)	
Hypertension*	No	6 (57.14%)	1 (42.86%)	0.468
	Yes	17 (17.4%)	6 (82.6%)	
Coronary Heart Diseases*	No	21 (77.8%)	6 (22.2%)	0.564
	Yes	2 (66.7%)	1 (33.3%)	
ESRD*	No	23 (79.3%)	6 (20.7%)	0.233
	Yes	0 (0%)	1 (100%)	

* Exact fisher test.

Association of severe symptoms with mortality of hemodialysis patients with COVID-19

The results from the exact Fisher test indicated that patients with cough complaints (P-Value = 0.128) and malaise (P-Value = 0.485) did not have a significant association with a higher mortality rate in ESRD patients with

COVID-19. Additionally, the exact Fisher test showed that other severe symptoms were not associated with the COVID-19 mortality rate in ESRD patients. These findings are summarized in Table 3.

Table 3. Examining the frequency and percentage of initial complaints and clinical manifestations of patients with COVID-19 based on the patient's outcomes

Symptoms	Yes/No	Recovered patients	Expired patients	P-value
Fever *	No	4 (66.7%)	2 (33.3%)	0.233
	Yes	19 (79.2%)	5 (20.8%)	
Cough *	No	22 (81.5%)	5 (18.5%)	0.128
	Yes	1 (33.3%)	2 (66.7%)	
Loss of consciousness *	No	22 (75.9%)	7 (24.1%)	0.616
	Yes	1 (100%)	0 (0%)	
Pain*	No	15 (75%)	5 (25%)	0.571
	Yes	8 (80%)	2 (20%)	
Dyspnea – Respiratory distress *	No	4 (80%)	1 (20%)	0.671
	No	19 (76%)	6 (24%)	
Malaise *	No	9 (81.8%)	2 (18.2%)	0.485
	Yes	14 (73.3%)	5 (26.3%)	
Anorexia *	No	14 (70%)	6 (30%)	0.228
	Yes	9 (76.7%)	1 (23.3%)	

* Exact fisher test.

Correlation of CRP serum levels with hemodialysis duration in hemodialysis patients with COVID-19

In this study, our findings revealed that the serum CRP levels did not correlate with hemodialysis duration (R = 0.267, P-Value = 0.154). In contrast, the obtained results from Spearman's correlation revealed the serum CRP levels had a significant negative correlation with ESRD in hemodialysis patients with COVID-19 (R = 0.527, P-Value < 0.003). Additionally, the results from Spearman's correlation indicated that the hemodialysis duration, PCR results, and CRP serum levels had no significant correlation with any type of pulmonary involvement in ESRD patients with COVID-19, which is diagnosed by chest CT graph (P-Value > 0.05).

Hemodialysis patients with COVID-19 outcomes

The CT scan results highlighted a significant difference between recovered and deceased ESRD patients with COVID-19. These findings are presented in Table 4.

Table 4. Mean and standard deviation of mortality and recovery in hemodialysis patients with COVID-19

Variables	Recovered patients	Expired patients	P-value
ESRD	2.00±0.00	1.85±0.37	0.00
PCR	1.30±0.47	1.57±0.53	0.365
CT graph	2.17±1.09	1.00±0.00	0.001
CRP	8.33±13.38	10.52±13.72	0.561

* Student T-test.

Discussion

This research aims to describe the clinical attributes and immediate repercussions experienced by a cohort of 30 chronic hemodialysis patients afflicted with COVID-19 in Gorgan province in 2019. The mean age of the participants stood at 58.97±11.88 years, signaling an elder populace in comparison to broader investigations encompassing hemodialysis patients, typically ranging between 57 and 66 years of age (3).

The clinical outcomes of this study show that the majority of hemodialysis patients with COVID-19 were discharged (86.6%), indicating effective acute management for most patients. However, the observed mortality rate of 13.4% highlights the significant impact of COVID-19 on this population. Bahat et al. reported a mortality rate of 20% among hemodialysis patients with COVID-19, with other studies indicating rates of 16% and 28% in groups of 37 and 25 hemodialysis patients, respectively (3,13). These rates were notably higher than the mortality rates observed in the general population, ranging from 0.8% to 1.4% (14-16). The elevated mortality in hemodialysis patients can be attributed to various factors, including concurrent diseases, chronic kidney failure, and immunosuppression induced by high uremia (17).

The clinical outcomes of this study indicate that the majority of hemodialysis patients with COVID-19 were discharged (86.6%), which indicates the effective acute management for most patients. However, the observed mortality rate of 13.4% underscores the severe impact of COVID-19 on this population. The increased susceptibility of men to the infection may be attributed to increased levels of ACE receptors, particularly in podocyte cells and proximal convoluted tubule cells that express the ACE2 and TMPRSS genes, which are the main targets of the SARS-CoV-2 virus. It is notable that kidney tissue exhibits greater ACE2 gene expression than lung tissue, with the binding affinity of SARS-CoV-2 receptors to ACE2 being 10 to 20 times higher than that of SARS-CoV-1 (9,17-19). Bwire et al. suggested that males were more susceptible to SARS-CoV-2 infection due to higher ACE2 receptor expression levels (20). Chai et al. (21) and Bwire et al. (20) provided evidence of increased ACE2 expression in male kidney tissues compared to females' kidney tissues, potentially contributing to the gender disparity in infection rates.

The strong association between diabetes and increased mortality emphasizes the critical need for effective management of these comorbidities to enhance clinical outcomes. Additionally, radiological abnormalities and the presence of ESRD are significant predictors of prognosis, highlighting the necessity for close monitoring and, when appropriate, more intensive therapeutic interventions. Xiong et al. (17) 95.4% of patients had at least one comorbidity, with cardiovascular disease associated with hypertension and diabetes being the most prevalent. Fisher et al. supported these findings and identified diabetes, hypertension, coronary artery disease, and pulmonary disease as the most common comorbidities among hemodialysis patients with COVID-19 (22). Li et al.'s study highlighted the predominance of high blood pressure and diabetes in ESRD patients with COVID-19. Furthermore, Li et al. emphasized the significance of respiratory diseases as additional common comorbidities in this patient population during the COVID-19 pandemic (23).

Clinical symptoms show a high incidence of fever (80%) and dyspnea (83.3%), indicating a severe COVID-19 disease course in hemodialysis patients. Radiological findings, particularly ground-glass opacities and bilateral consolidations, further emphasize the significant pulmonary involvement in this vulnerable group. Our findings are in the same direction as Valeri et al., Fisher et al., and Xiong et al., where fever consistently emerged as the primary clinical symptom, followed by cough, fatigue, and shortness of breath in patients with COVID-19 (17,18,22). Adwan et al. corroborated these clinical observations, highlighting fever, respiratory distress, and fatigue as the most prevalent symptoms among hemodialysis patients with COVID-19 (24). On the other hand, Valeri et al. found one-sided opacity in 10% of patients in chest radiographs, with over half of the recovered patients showing multiple or one-sided infiltrations (18). Goicoechea and Ma reported a ground glass radiological appearance with bilateral and peripheral patterns in 85.7% and 64% of patients, respectively (25,26).

In our study, comparison of clinical and laboratory parameters between discharged and deceased hemodialysis patients with COVID-19 demonstrated that non-survivors were generally older and exhibited elevated white blood cell counts and serum creatinine levels relative to recovered patients. Other laboratory values showed no significant differences between groups. Comorbidities such as diabetes were more common among the deceased patients, and their clinical presentation, including symptoms like weakness and lethargy, differed significantly from survivors (27). These findings are consistent with the research by Zhou et al. (2020), which reported higher mortality rates associated with comorbid conditions prevalent in hemodialysis patients, thus validating our results (28).

Laboratory analyses revealed that elevated white blood cell counts and serum creatinine levels were significant prognostic indicators associated with mortality. The absence of notable differences in other laboratory parameters underscores the need for further research to identify additional predictive biomarkers. In Valeri et al.'s study, a 14-day follow-up showed that 18 patients (31%) died within six days of hospital admission. Deceased patients had significantly higher baseline levels of white blood cells, lactate dehydrogenase (LDH), and C-reactive protein (CRP) compared to survivors (P-Value = 0.04) (18). Ma et al. involving 230 hemodialysis patients in Wuhan, China, 15 individuals (6.25%) died from COVID-19, with cardiovascular disease, cerebrovascular disease, and hyperkalemia identified as leading causes of death (29). Laboratory findings reveal that elevated WBC counts and creatinine levels serve as significant prognostic markers associated with mortality (19). Findings from Valeri's, Yiqiong et al.'s, and Fisher's studies further support the adverse prognostic indicators identified in our research, including elevated inflammatory markers and underlying cardiovascular conditions.

This study showed a significant relationship between some demographic factors, comorbidities, symptoms, and laboratory findings with patient outcomes. For example, increased WBC count and creatinine level were identified as important prognostic markers associated with mortality. In addition, comorbidities such as diabetes were strongly associated with increased mortality rates. These findings emphasize the importance of comprehensive patient assessment and appropriate treatment strategies to optimize outcomes in this vulnerable population.

Despite the lack of long-term follow-up data, this study provides valuable insights into the acute effects of COVID-19 on hemodialysis patients. Future research should include long-term follow-up to assess ongoing outcomes and potential complications. Additionally, larger, multicenter studies are needed to validate these findings and explore further factors influencing outcomes in this vulnerable population. Enhanced preventive measures, early interventions, and regular monitoring using CT scans and laboratory markers are crucial for managing hemodialysis patients with COVID-19.

Conclusion

In summary, this study highlights the clinical outcomes of hemodialysis patients with COVID-19. While most patients were discharged, a notable mortality rate underscores the severity of the disease. Common symptoms and significant

radiological findings emphasize the acute presentation of COVID-19 in this population. Laboratory markers, especially elevated WBC counts and creatinine levels, serve as important prognostic indicators. Management of comorbid conditions like diabetes is crucial, and the study underscores the need for vigilant monitoring and potentially more aggressive treatment strategies. Further research is warranted to validate these findings and explore additional factors affecting outcomes in hemodialysis patients with COVID-19.

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Ethical statement

Ethical approval was obtained from the Golestan University research committee, under approval number IR.GOUMS.REC.1399.377. Written informed consent was obtained from all patients or their legal guardians before their inclusion in the study. All patient data were anonymized to ensure privacy and confidentiality.

Conflicts of interest

The authors have no financial or proprietary interests in any material discussed in this article.

Author contributions

The role of each participant is as follows: SA and MM conceived this study and were the supervisors. SJ, and AR. collected and analyzed the data. Also, ZM and AR. drafted the manuscript. All authors read and approved the final version of the manuscript.

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