Research Article

Risk Factors for Severe Course and Mortality in Hemodialysis Patients with COVID-19

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Abstract

Patients undergoing Chronic Hemodialysis (CHD) treatment are among the most vulnerable and affected groups by Coronavirus disease 2019 (COVID-19). Multiple factors such as comorbidities, altered immune response, and insufficient anti-epidemic measures determine a higher risk of infection, complicated course of the disease requiring intensive treatment, and high mortality in these patients. The aim of this study is to identify the risk factors for a more severe course and mortality in patients hospitalized in the Nephrology Department of "St. George" University Hospital, Plovdiv with COVID-19 infection undergoing hemodialysis treatment for end-stage Chronic Kidney Disease (CKD). A retrospective observational study was conducted, including 114 patients, 27 of whom were on hemodialysis. In CHD patients, the lethality rate is 33.3%, or 90.0% of the deaths in the overall sample of patients with COVID-19. It was found that the presence of cardiovascular disease (p=0.046), intensive care unit stay (p=0.008), and high levels of C-reactive protein, lactate dehydrogenase, and ferritin (p=0.009, 0.029, 0.021 respectively) in CHD patients correlate with high mortality Additionally, statistically significant differences in laboratory parameters were found between CHD patients and patients without CKD with severe COVID-19 infection, assessed using the CURB65 scale. Some indicators used as predictors in the general population may not be applicable in dialysis patients. Identifying and monitoring risk factors could aid in the prediction and timely determination of the risk of a more severe course and prognosis in CHD patients.

Keywords: Clinical course; Coronavirus; Dialysis; Mortality

Introduction

Coronavirus disease 2019 (COVID-19) has impacted patients with kidney disease on multiple levels. Acute Kidney Injury (AKI) is a common complication among hospitalized COVID-19 patients and is associated with high mortality. Furthermore, the incidence of severe COVID-19 infection is high among patients with Chronic Kidney Disease (CKD), especially those undergoing Chronic Hemodialysis (CHD), with a correspondingly high mortality rate [1,2]. Comorbidities such as Diabetes Mellitus (DM), Arterial Hypertension (AH), Cardiovascular Diseases (CVD), and advanced age pose a high risk for developing severe illness in these patients [3]. Hemodialysis patients have an abnormal immune response due to uraemia, which results in both impaired immunity and a pro-inflammatory state [2]. CHD patients on immunosuppressive therapy exhibit a suppressed immune response. Moreover, even those not on immunosuppressants show a weaker antibody response compared to the general population, making them more susceptible to infections [4]. In addition, anti-epidemic measures applied to the general population often cannot be implemented for these patients due to the need for transportation to and from closed dialysis units, frequently using public or shared transport, which increases the risk of infection [5]. A meta-analysis of 12 studies including 3,867,367 patients concluded that CKD patients with COVID-19 had a 5.81-fold higher mortality rate compared to CKD patients without COVID-19 infection, which is significantly higher than the mortality in the general population as reported by the World

Health Organization [2,6]. In contrast to the general population, individuals undergoing hemodialysis consistently exhibit unique patterns in inflammation- related laboratory markers, heightened cardiovascular risk, and elevated mortality rates due to kidney failure, dialysis treatment, and comorbidities [7]. These factors complicate the interpretation of certain established risk factors for severe disease progression and mortality from COVID-19 in the general population.

The aim of this study is to identify the risk factors for severe disease progression and mortality among patients with COVID-19 undergoing hemodialysis for end-stage kidney disease.

Material and Methods

A retrospective observational study was conducted over 18 months (from 01 December 2020 to 31 March 2022) among patients undergoing hemodialysis for end-stage CKD and diagnosed with COVID-19, treated in the Nephrology clinic of "Sv. Georgi" University Hospital, Plovdiv, Bulgaria.

Eligibility Criteria

Inclusion criteria: COVID-19 diagnosis confirmed by RT-PCR for SARS-CoV-2, age over 18 years, signed informed consent.

Exclusion criteria: Patients < 18 years of age, patients that declined to sign informed consent, patients with AKI.

The patients were divided into two groups—patients on CHD for end-stage CKD and patients without CKD.

The following characteristics were examined in both groups:

Demographic: gender and age

Clinical and laboratory indicators: severity of COVID-19 infection, length of hospital stay, need for intensive care, the need of oxygen supplementation, neutrophils, lymphocytes, neutrophil/lymphocyte ratio, C-Reactive Protein (CRP), D-Dimer (DD), ferritin, Lactate Dehydrogenase (LDH).

Comorbidities: Diabetes mellitus, arterial hypertension, and cardiovascular diseases— ischemic heart disease and heart failure.

To assess the severity of COVID-19 infection, the CURB-65 scoring system was used with the following parameters: confusion (C), urea >7 mmol/L (U), respiratory rate >30/min (R), blood pressure <90/60 mmHg (B), and age >65 years (65). Each criterion counts as 1 point, with a maximum score of 5. Since patients on hemodialysis have elevated urea levels, we excluded this criterion. A CURB-65 score of ≥3 was considered severe, and ≤2 was considered mild to moderate COVID-19. The data on the examined parameters were collected from the hospital information system and from the patients' medical history records.

Statistical analysis

Categorical variables are presented as frequency and percentage; proportions were compared using the chi-square test and Fisher's exact test. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data and compared using the t-test. $p < 0.05$ was considered statistically significant. Data were statistically processed using SPSS version 23.0 (SPSS Inc., USA).

Results

Demographic, Clinical Characteristics and Comorbidities

A total of 114 patients met the inclusion criteria. Of these, 23.68% (n=27) were undergoing chronic hemodialysis, while the remaining 76.32% (n=87) had no Chronic Kidney Disease. The demographic and clinical characteristics of the included patients are presented in Table 1.

Demographic and clinical characteristics (n=114)		
Age, mean±SD		62.75±14.61
Gender, n (%)	male	57 (50%)
	female	57 (50%)
O_2-therapy, n (%)	yes	55 (48.2%)
	no	59 (51.8%)
Arterial hypertension, n (%)	yes	80 (70.2%)
	no	34 (29.8%)
Diabetes mellitus, n (%)	yes	17 (14.9%)
	no	97 (85.1%)

Cardiovascular disease, n (%)	yes	34 (29.8%)
	no	80 (70.2%)
Paraclinical characteristics, mean±SD		
Ly (22-48%)		15.36±10.02
Neu (42-70%)		77.44±11.79
Neu/Ly (1-3)		8.70 ±8.67
CRP (0-10 mg/L)		112.86±91.81
DD (0-0.50 mg/L)		9.94±60.27
LDH (230-460 U/L)		802.19±452.22
Ferritin (23.9-336.2 ng/ml)		745.66±535.13
Clinical course and outcome		
Hospital stay days, mean±SD		11.65±5.99
Deceased, n (%)	yes	10 (8.8%)
	no	104 (91.2%)
ICU admission, n (%)	yes	8 (7.0%)
	no	106 (93.0%)
CURB65 score. Mean, n (%)	≤2	51 (44.7%)
	≥3	63 (55.3%)

Abbreviations: SD: Standard Deviation; Ly: Lymphocytes; Neu: Neutrophiles; Neu/Ly: Neutrophile/Lymphocyte Ratio; CRP: C-Reactive Protein; DD: D-Dimer; LDH: Lactatedehydrogenase; ICU: Intensive Care Unit

Table 1: Demographic, clinical characteristics and comorbidities.

The differences between patients on CHD and patients without CKD are shown in Table 2.

		CHD (n=27)	No CHD (n=87)	*p*
Demographic and clinical characteristics				
Age, mean±SD		64.7±13.25	62.15±15.03	0.430*
Gender, n (%)	male	20 (35.1%)	37 (64.9%)	0.007
	female	7 (12.3%)	50 (87.7%)	
O$_2$-therapy, n (%)	yes	20 (36.4%)	35 (63.6%)	0.004
	no	7 (11.9%)	52 (88.1%)	
Arterial hypertension, n (%)	yes	23 (28.8%)	57 (71.3%)	0.057
	no	4 (11.8%)	30 (88.2%)	
Diabetes mellitus, n (%)	yes	12 (70.6%)	5 (29.4%)	<0.001
	no	15 (15.5%)	82 (84.5%)	
Cardiovascular disease, n (%)	yes	13 (38.2%)	21 (61.8%)	0.029
	no	14 (17.5%)	66 (82.5%)	
Paraclinical characteristics, mean±SD				

Lymphocytes, Ly (22-48%)		10.06±6.50	17.05±10.38	0.001*
Neutrophiles, Neu (42-70%)		84.65±8.40	75.15±11.83	<0.001*
Neutrophile/lymphocyte ratio, Neu/Ly (1-3)		14.26±11.22	6.93±6.88	<0.001*
C-reactive protein, CRP (0-10 mg/L)		162.90±103.22	97.33±82.61	0.001*
D-dimer, DD (0-0.50 mg/L)		5.55±7.10	11.32±69.01	0.666*
Lactatedehydrogenase, LDH (230-460 U/L)		1055.33±597.83	722.71±365.23	0.001*
Ferritin (23.9-336.2 ng/ml)		1209.00±498.40	570.69±437.07	<0.001*
Clinical course and outcome				
Hospital stay - days, mean±SD		13.15±8.46	11.18±4.97	0.138*
Deceased, n (%)	yes	9 (90.0%)	1 (10.0%)	<0.001
	no	18 (17.3%)	86 (82.7%)	
ICU admission, n (%)	yes	6 (75.0%)	2 (25.0%)	0.002
	no	21 (19.8%)	85 (80.2%)	
CURB65 score, Mean, n (%)	≤2	5 (9.8%)	46 (90.2%)	0.002
	≥3	22 (34.9%)	41 (65.1%)	

Notes: p – Fisher's Exact Test, p* – t-test; **Abbreviations:** CHD: Chronic hemodialysis; CKD: Chronic kidney disease; SD: Standard Deviation; ICU: Intensive Care Unit

Table 2: Comparison of dialysis and non-dialysis patients.

The average age of CHD patients was 64.7 years (±13.251), with the majority being male (74.07%). There were no statistically significant differences in age between patients on dialysis and non-CKD. However, a significant difference in patients' gender was found between groups (p=0.007).

Comorbidities in the CHD group included arterial hypertension in 85.2%, diabetes mellitus in 44,4%, and cardiovascular disease in 48.1%. As expected, a statistically significant difference was found regarding diabetes (p<0.001) and cardiovascular disease (p=0.029) between the groups. The majority of patients in the non-CKD group did not have diabetes or CVD.

In both patient cohorts, all monitored laboratory parameters exceeded the upper reference limits, with the exception of lymphocytes in the CHD group, which were reduced. All laboratory parameters showed statistically significant differences between the groups, except for DD. A statistically higher value of lymphocytes was observed in non-CKD group compared to the CHD patients (p=0.001). Regarding all other parameters, significantly higher values were observed among the dialysis patients, as detailed below: CRP (p=0.001), LDH (p=0.001), ferritin (p<0.001), neutrophiles (p<0.001), neutrophile/lymphocyte ratio (p<0.001).

A total of 51 patients (40.73%) had mild or moderate COVID-19, while 63 (59.29%) had severe infection. A statistically significant difference was found in the severity of COVID-19 between the two groups (p=0.002). The majority of CHD patients—81.5%—had severe SARS-CoV infection (CURB-65 score ≥3), while most patients in the non-CKD group had a CURB-65 score below 2.

The overall mortality rate in the sample was 8.8% (n=10), distributed as follows: 90.0% (n=9) among dialysis patients and 10.0% (n=1) among non-CKD patients. A statistically significant difference was found between the two groups regarding mortality (p<0.001). This corresponds to a case fatality rate of 33.3% (9/27) in the CHD group versus 1.1% (1/87) in the non-CHD group—a 30-fold increase in relative risk.

A significant difference was also observed in the need for oxygen therapy (p=0.004), with 74.1% of the dialysis patients requiring oxygen therapy, while 59.8% in the other group did not.

No statistically significant difference was found in total hospital stay duration; however, the average length of stay was longer (13.15 days, mean) for CHD patients. Statistical significance was observed in terms of ICU admission (p=0.002), with over 93% of patients not requiring ICU care. Of the eight patients who necessitated ICU admission, six (75.0%) belonged to the CHD group. This translates to an ICU admission rate of 22.2% (6/27) in

CHD patients versus 2.3% (2/87) in non-CHD patients, representing a nearly 10-fold difference.

Risk Factors for More Severe COVID-19 in Patients on Chronic Hemodialysis

Most dialysis patients had severe COVID-19 infection, and only a small proportion had mild COVID-19. Therefore, we did not evaluate the difference within the CHD group. However, we did examine the difference in severe COVID infection between dialysis and non-dialysis patients. Table 3 presents the comparison between both groups of patients with severe COVID-19 infection classified according to the CURB-65 scale.

		CHD (n=22)	No CHD (n=41)	p
Demographic and clinical characteristics				
Age, mean±SD		66.50±12.43	66.54±12.75	0.991*
Gender, n (%)	male	17 (53.1%)	15 (46.9%)	0.003
	female	5 (16.1%)	26 (83.9%)	
O_2-therapy, n (%)	yes	17 (41.5%)	24 (58.5%)	0.172
	no	5 (22.7%)	17 (77.3%)	
Arterial hypertension, n (%)	yes	20 (40.8%)	29 (59.2%)	0.111
	no	2 (14.3%)	12 (85.7%)	
Diabetes mellitus, n (%)	yes	10 (76.9%)	3 (23.1%)	0.001
	no	12 (24.0%)	38 (76.0%)	
Cardiovascular disease, n (%)	yes	10 (41.7%)	14 (58.3%)	0.423
	no	12 (30.8%)	27 (69.2%)	
Paraclinical characteristics, mean±SD				
Lymphocytes, Ly (22-48%)		8.73±5.75	14.38±7.41	0.003*
Neutrophiles, Neu (42-70%)		86.37±7.97	78.59±9.72	0.002*
Neutrophile/lymphocyte ratio, Neu/Ly (1-3)		16.19±11.54	7.41±4.47	<0.001*
C-reactive protein, CRP (0-10 mg/L)		178.36±106.12	120.90±81.78	0.020*
D-dimer, DD (0-0.50 mg/L)		6.48±7.58	20.23±99.59	0.522*
Lactatedehydrogenase, LDH (230-460 U/L)		1068.96±622.22	793.17±440.51	0.045*
Ferritin (23.9-336.2 ng/ml)		1201.76±519.03	644.94±493.69	<0.001*
Clinical course and outcome				
Hospital stay - days, mean±SD		11.93±5.69	13.86±9.18	0.305*
Deceased, n (%)	yes	8 (88.9%)	1 (11.1%)	0.001
	no	14 (25.9%)	40 (74.1%)	
ICU admission, n (%)	yes	5 (71.4%)	2 (28.6%)	0.045
	no	17 (30.4%)	39 (69.6%)	
Notes: p – Fisher's Exact Test, p* – t-test; **Abbreviations:** CHD: Chronic Hemodialysis; SD: Standard Deviation; ICU: Intensive Care Unit				

Table 3: Patients with severe infection, CURB65≥3.

Statistically significant differences were observed in gender (p=0.003), where more than 75% of the hemodialysis patients with severe COVID were men. Results similar to those of previous analyses were observed in the laboratory parameters.

All monitored laboratory parameters in both patient groups were elevated above the upper reference limits, except for lymphocytes in the hemodialysis patients, which were decreased. All laboratory parameters showed statistically significant differences between the groups, except for D-dimer. A statistically significant higher value of lymphocytes was found in the non-CKD group compared to the hemodialysis patients (p=0.003), while for all other parameters, statistically higher values were observed in the dialysis group, as follows: CRP (p=0.020), LDH (p=0.045), ferritin (p<0.001), neutrophiles (p<0.001), neutrophile/lymphocyte ratio (p<0.001).

Of the 10 deceased patients, 9 had severe COVID-19. There was a significant difference in mortality between the two groups (p=0.001). However, it should be noted that some of the statistically significant differences observed may be due to the previously mentioned fundamental disparities between dialysis and non-CKD patients or to sample heterogeneity.

Risk Factors for COVID-19 Mortality in Patients on Chronic Hemodialysis

To identify the risk factors for mortality, we compared deceased and surviving patients within the dialysis group. Table 4 compares indicators among patients undergoing CHD according to their COVID-19 outcome.

		Deceased (n=9)	Survivors (n=18)	*p*
Demographic and clinical characteristics				
Age, mean±SD		63.50±16.09	67.11±3.30	0.515*
Gender, n (%)	male	8 (40.0%)	12 (60.0%)	0.363
	female	1 (14.3%)	6 (85.7%)	
O$_2$-therapy, n (%)	yes	9 (45.0%)	11 (55.0%)	0.059
	no	0 (0.0%)	7 (100.0%)	
Arterial hypertension, n (%)	yes	8 (34.8%)	15 (65.2%)	1.000
	no	1 (25.0%)	3 (75.0%)	
Diabetes mellitus, n (%)	yes	6 (50.0%)	6 (50.0%)	0.127
	no	3 (20.0%)	12 (80.0%)	
Cardiovascular disease, n (%)	yes	2 (14.3%)	12 (85.7%)	0.046
	no	7 (53.8%)	6 (46.2%)	
Paraclinical characteristics, mean±SD				
Lymphocytes, Ly (22-48%)		9.13±5.22	10.52±7.14	0.612*
Neutrophiles, Neu (42-70%)		86.87±8.26	83.54±8.47	0.342*
Neutrophile/lymphocyte ratio, Neu/Ly (1-3)		14.82±11.51	13.98±11.40	0.858*
C-reactive protein, CRP (0-10 mg/L)		233.72±91.42	127.49±91.54	0.009*
D-dimer, DD (0-0.50 mg/L)		6.96±4.69	4.85±8.07	0.478*
Lactatedehydrogenase, LDH (230-460 U/L)		1404.67±505.01	880.67±574.18	0.029*
Ferritin (23.9-336.2 ng/ml)		1539.00±197.55	1063.77±525.03	0.021*
Clinical course and outcome				
Hospital stay - days, mean±SD		13.00±4.90	13.44±13.46	0.901*
ICU admission, n (%)	yes	5 (83.3%)	1 (16.7%)	0.008
	no	4 (19.0%)	17(81.0%)	

CURB65 score, Mean, n (%)	≤2	1 (20.0%)	4 (80.0%)	0.636
	≥3-5	8 (36.4%)	14(63.6%)	
Notes: p – Fisher's Exact Test, p* – t-test; **Abbreviations:** SD: Standard Deviation; ICU: Intensive Care Unit				

Table 4: Patients on hemodialysis and clinical outcome.

No statistically significant differences were observed in the demographic variables or in arterial hypertension and diabetes. However, a significant difference was found among patients with cardiovascular disease (p=0.046); 77,8% of the deceased had cardiovascular disease, while 66.7% of the survivors did not.

Regarding laboratory parameters, statistically significant differences were found in CRP (p=0.009), LDH (p=0.029), and ferritin (p=0.021). C-reactive protein was markedly elevated in deceased patients (233.72 ± 91.42 mg/L vs. 127.49 ± 91.54 mg/L, p=0.009), representing an 83% increase over survivors. The level of CRP elevation in deceased patients was substantially higher than in the overall CHD cohort (162.90 mg/L).

Lactate dehydrogenase was 60% higher in deceased patients (1404.67 ± 505.01 U/L vs. 880.67 ± 574.18 U/L, p=0.029). Non-survivors demonstrated mean LDH exceeding 1400 U/L, more than triple the normal upper limit and substantially higher than the overall CHD mean (1055 U/L). Serum ferritin was 45% higher in deceased patients (1539.00 ± 197.55 ng/mL vs. 1063.77 ± 525.03 ng/mL, p=0.021). Deceased patients exhibited mean ferritin approaching 1540 ng/mL, nearly 4.6-fold above the normal upper limit (336.2 ng/mL).

Among the clinical characteristics, a statistically significant difference was found in ICU admissions: 83.3% of patients admitted to the ICU died (p=0.008). Conversely, 94.4% of patients who were not admitted to the ICU survived.

Discussion

Chronic Kidney Disease and COVID-19 are linked in a complex manner. COVID-19 can result in acute kidney injury and potentially lead to a progressive decline in kidney function, which may exacerbate or contribute to the development of CKD [8,9]. Notably, patients with CKD are among the most vulnerable to and significantly affected by COVID-19. According to a WHO report, there is an approximate 1% global mortality rate due to COVID-19, while data from the U.S. dialysis registry reported a 24.9% mortality rate among CHD patients [10,11]. Additionally, according to the Spanish COVID-19 CKD Working Group Registry, mortality is 6.2 times higher in dialysis patients compared to the general population [12]. Data pooled from multiple sources show that mortality rates in hemodialysis patients infected with COVID-19 range from approximately 23.8% to 28.3%. This represents a 20-30 times higher mortality compared to the normal population and a substantial increase compared to dialysis [13]. The mortality risk across different stages of Chronic Kidney Disease is not the same. As kidney disease advances, the risk of death increases, with the highest risk observed in patients undergoing kidney replacement therapy.

Artborg, et al. conducted a study with an aim to investigate the association between CKD stage, dialysis modality, and risk of severe COVID-19. This study included 7856 non- dialysis CKD patients and 4018 dialysis patients. The adjusted odds ratios for COVID-19 hospitalization and mortality were highest in the dialysis group, followed by CKD 4, as compared with CKD 3b. Dialysis patients had the highest risk of COVID-19-related death, indicating more than three times the risk compared to patients with less severe CKD stages [14]. This higher vulnerability among dialysis patients originates from multiple factors such as underlying comorbid conditions common in dialysis populations, basal hyperinflammation, dysregulation of immune function due to uremia, the dialysis procedure itself and frequently inadequate implementation of infection control measures. Collectively, these elements elevate the likelihood of acquiring COVID-19 infection, increase the probability of developing severe disease, leading to intensive medical interventions, and subsequently elevate mortality risk compared to the general population.

The data obtained from our study are consistent with previously published results and reflect the more severe course and higher mortality rate among chronic hemodialysis patients with COVID-19. The mortality rate among CHD patients who were admitted in our department was 33.3% and most of them had severe COVID-19. Identifying the factors that influence mortality and severity of COVID-19 in dialysis patients is of great importance.

Age, Gender and Comorbidities as Risk Factors for Severe Course and Mortality in Hemodialysis Patients with COVID-19

Several risk factors have been linked with more severe COVID-19 infection. Hypertension, diabetes, and CVD are independently associated with severe COVID-19 and, together with age and male sex, can be informative for predicting the risk of severe COVID-19 [2,7,15]. A large meta-analysis involving 2,898 CHD patients showed that survivors were significantly younger than those

who died [2]. He et al. found a strong association between age and mortality, suggesting that patients undergoing hemodialysis who are older than 66.5 have a higher risk of death and poorer prognosis [16]. Another study had a different age cut off of 74.8 years, demonstrating greater mortality risk [12]. In our study, we also observed that deceased patients were older, although this was not statistically significant.

Data from different studies indicate that two-thirds of deceased patients were male. The ERACODA Collaboration Study of 768 dialysis patients with COVID-19 found that 64% of deceased patients were male [17]. In our study, male sex among CHD patients was associated with a more severe course of infection compared to non-dialysis patients (p=0.003). We also found that more than 86.7% of female patients survived, suggesting that gender likely plays a significant role in determining both the severity and clinical outcome of COVID-19 in dialysis patients.

CVD was only statistically significantly associated with severe COVID-19 and deceased patients, identifying it as a risk factor for worse outcomes and prognosis [2,18]. Patients with CVD and COVID-19 had a 4-fold higher risk of death. CVD mortality in general CKD patients during COVID-19 was 11.1% vs. 2.7% in non-CKD patients [19,20]. In our study, we demonstrated that pre-existing cardiovascular disease was a significant risk factor for mortality in dialysis patients with COVID-19 infection, being present in 77.8% of fatal cases.

Several studies have found diabetes to be statistically linked with increased mortality in COVID-19 patients, with hazard ratios around 1.52, indicating a 52% higher risk [21]. Patients with diabetic nephropathy had nearly a twofold rate of COVID-19 pneumonia, a higher probability of admission, a twofold probability of intubation, and a higher case-fatality rate once admitted compared to patients with CKD alone [22].

However, a meta-analysis including 18,822 patients showed that diabetes in CKD patients with COVID-19 was associated with an increased risk of mortality, but the subgroup analysis showed that diabetes was not associated with mortality in the HD group [23]. We identified a statistically significant link between the occurrence of DM in patients with severe COVID-19 undergoing hemodialysis and those without accompanying CKD. Conversely, our data did not show that diabetes is a risk factor for mortality.

Clinical and Laboratory Parameters as Risk Factors for Severe Course and Mortality in Hemodialysis Patients with COVID-19

Hemodialysis patients exhibit unique laboratory marker profiles compared to the general population due to alterations caused by kidney failure and dialysis treatment. These patients consistently show elevated inflammatory markers, altered lipid profiles,

and increased cardiovascular risk attributed to this chronic inflammation [24]. For instance, ferritin levels are typically higher in the CHD cohort, and recommended ferritin levels in dialysis levels are 200-500 ng/mL [25,26]. CRP elevation is endemic in dialysis patients, with 30-50% of hemodialysis patients having CRP >3 mg/L [27]. D-dimer levels are also commonly elevated in dialysis patients, even in the absence of additional diseases. In a study of chronic hemodialysis patients, the median D-dimer level was 966 µg/L, with 75% of patients having levels above the typical positive cut off of 500 µg/L [28]. Dialysis patients typically have an increased neutrophil-to-lymphocyte ratio compared to healthy controls and even non-dialysis CKD patients [29].

Some of the most commonly used markers for assessing the risk of mortality and/or the development of severe COVID-19 infection are neutrophil/lymphocyte ratio, C-reactive protein, D-dimer, ferritin, and LDH [30]. While these laboratory parameters are typically elevated in patients undergoing dialysis, multiple studies have demonstrated their value as prognostic markers for COVID-19 outcomes within this population, including the prediction of severe disease and increased mortality risk [2]. A study by Goicoechea, et al. showed that nonsurvivor CHD patients had higher LDH and higher CRP levels than patients who survived [31]. Increased LDH levels have been associated with worse clinical outcomes and progression to severe disease requiring ICU admission or mechanical ventilation [32]. Statistically significant elevations were observed in hemodialysis patients with severe COVID-19, as well as in those who died, showing values nearly double those seen in patients who recovered. In all our analyses, ferritin levels were significantly higher in dialysis patients compared to others. Similar to a systematic review and meta-analysis by Riani et al., it was observed that there is a statistically significant difference between the deceased and surviving CHD patients with COVID-19, with higher levels in the deceased group [33]. Independent predictors of mortality are CRP levels upon admission and maximum CRP values during hospitalization. A threshold value for CRP upon admission, established at 56.5 mg/dL, shows a sensitivity of 69.7% and specificity of 67.5% for mortality prediction. Conversely, the threshold value for maximum CRP during hospitalization, set at 108.15 mg/dL, demonstrates a sensitivity of 82.4% and specificity of 76.2% for predicting mortality [34]. In our study, hemodialysis patients who died had the highest CRP values, and statistically significantly higher values compared to survivors, which demonstrates the importance of CRP as a significant risk factor for mortality among dialysis patients with COVID-19.

Alongside ferritin and CRP, other markers such as D-dimer and the neutrophil-to-lymphocyte ratio (NLR) are frequently elevated, further underscoring the persistent inflammatory state in this population. Lymphopenia is more common in severe cases and is linked to higher mortality [10]. Rista et al. report that lymphopenia

is found to be one of the most significant predictors of mortality in hemodialysis patients with COVID-19 [35]. Regardless, our study did not find a statistically significant difference between survivors and non-survivors.

A study with COVID-19-positive hemodialysis patients found mean D-dimer levels of around 1172 ng/mL, which did not show a statistically significant correlation with age or dialysis duration but were higher than typical baseline levels in dialysis patients. D-dimer levels in these patients also showed a positive correlation with inflammatory markers like CRP and a negative correlation with platelet and lymphocyte counts, although these correlations were not statistically significant. Factors independently associated with higher D- dimer levels included age over 65, dialysis via catheter access, and elevated CRP indicating inflammation [36]. Elevated D-dimer levels are linked to adverse clinical outcomes, increased need for mechanical ventilation, and higher mortality in the general population, and they also serve as risk factors for mortality in dialysis patients with COVID-19 [31,33,37]. However, it should be noted that there is evidence indicating that D-dimers can be cleared by dialysis therapy, which in turn may affect their concentration [31].

However, in our study, we found no statistically significant differences in D-dimer levels between the general and dialysis populations, nor did D-dimer levels correlate with clinical outcomes among HD patients. The observed lower average D-dimer levels in the CHD group in our clinic may be due to the additional doses of LMWH administered during the course of COVID-19 on top of the regular use of systemic anticoagulation during dialysis procedures and/or the vascular access (most of the patients in the study had an AV fistula) [38].

Finally, the severity of illness in patients with COVID-19 undergoing dialysis is further reflected in their elevated ICU admission rates and corresponding mortality levels. A meta-analysis found that about one-third of patients with severe COVID-19 in the general population require admission to the ICU. A systematic review covering 145 studies demonstrated that ICU admission among dialysis patients was associated with high mortality (42.8–100%) [39]. Our study also confirms a high frequency of ICU admission among dialysis patients compared to patients without CKD, as well as a statistically significant difference in this criterion between survivors and deceased CHD patients. In our study, 83.3% of deceased patients required intensive care compared to only 16.7% of survivors.

The high ICU mortality (83.3%) in this cohort was considerably higher compared to general COVID-19 ICU mortality rates (typically 30-50%), underscoring the poor prognosis once hemodialysis patients develop critical illness [40]. This suggests that ICU admission may represent a point of no return for many dialysis patients, as their chances of survival sharply decline, possibly due to inability to tolerate mechanical ventilation, propensity for ventilator- associated complications, hemodynamic instability during dialysis procedures, or irreversible multi-organ failure.

Conclusion

The COVID-19 pandemic posed new and serious challenges for dialysis patients and dialysis centers worldwide. This study emphasizes the unique characteristics of dialysis patients, the characteristic deviations regarding changes in laboratory parameters, and the notably higher mortality in the dialysis group compared to the non-CKD group. The observed outcomes and patterns highlight the disease's impact on dialysis patients, confirming a high rate of ICU admissions, more severe illness, and increased mortality. While standard COVID- 19 risk markers apply to dialysis populations, their interpretation must account for the unique baseline laboratory abnormalities characteristic of end-stage renal disease. Nevertheless, the main laboratory markers for assessing risk of disease progression and mortality are also useful in dialysis patients. Monitoring these factors may help predict disease progression and prognosis in patients undergoing chronic hemodialysis [41].

Limitations

Our study has several limitations. First, the retrospective design inherently introduces potential biases, such as selection bias and information bias, which may affect the validity and generalizability of the findings. Second, the relatively small sample size limits the statistical power of the study, reducing the ability to detect significant associations or differences. This constraint also restricts the extent to which the findings can be generalized to broader populations or different settings. Additionally, a statistically significant difference in gender distribution was observed, which could introduce bias or confounding effects if gender-related factors influence the outcomes studied. Recognizing these limitations is essential for contextualizing the study's contributions and guiding subsequent investigations to build on these preliminary findings.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and approved by the Commission on Academic Ethics of MU of Plovdiv (Session №8 and date of approval 9 July 2025; P-KHE-22/22.08.2025). Written informed consent has been obtained from all patients involved in this study.

Consent for Publication

Written informed consent for publication was obtained from all participants.

Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article. All authors have agreed on the journal to which the article will be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage and agree to take responsibility and be accountable for the contents of the article.

Disclosure

The authors report no conflicts of interest in this work.

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