Coronavirus Pandemic

Predictors of mortality in hemodialysis patients with COVID-19: A single-center experience

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Abstract

Introduction: The COVID-19 pandemic has disproportionately affected patients with preexisting comorbidities, particularly dialysis patients. The aim of this study was to determine predictors of mortality in this population.

Methodology: We conducted an observational, retrospective, cohort study collecting data from pre and post-vaccine from the electronic medical records of a single dialysis center at Hygeia International Hospital Tirana, Albania.

Results: Of 170 dialysis patients, 52 were diagnosed with COVID-19. The prevalence of COVID-19 infection in our study was 30.5%. The mean age was 61.5 ± 12.3 years and 65.4% were men. The mortality rate in our cohort was 19.2%. Mortality rates were higher in patients with diabetic nephropathy ($p < 0.04$) and peripheral vascular disease ($p < 0.01$). Elevated C- reactive protein (CRP) ($p < 0.018$), high red blood cell distribution width (RDW) ($p < 0.03$), and low lymphocyte and eosinophil counts, were found to be risk factors for severe COVID-19 disease. ROC analysis identified lymphopenia and eosinopenia as the strongest predictors of mortality. After the vaccine administration, the mortality rate in the vaccinated population was 8%, in contrast to the 66.7% mortality rate that was found in the unvaccinated group ($p < 0.001$).

Conclusions: Our study revealed that risk factors for the development of severe COVID-19 infection were RDW, low lymphocyte and eosinophil counts, elevated levels of CRP. Lymphopenia and eosinopenia were determined as the most important predictors of mortality, in our cohort. Mortality was notably lower among vaccinated patients.

Key words: COVID-19; hemodialysis; mortality; vaccine; Albania.

Introduction

The SARS-CoV-2/COVID-19 pandemic has posed unprecedented challenges to healthcare systems and personnel around the world, in terms of providing optimal care to all affected patients. It has been particularly strenuous for nephrology specialists that have had to attend to a very fragile and high-risk population. Presently, more than 6.3 million deaths have been reported worldwide [1]. The cumulative experience of these past two years has established numerous risk factors associated with higher mortality rates in the general population, including advanced age, male sex, obesity, diabetes, hypertension and other cardiovascular pathologies, chronic pulmonary disorders, chronic kidney disease, and malignancy [2,3]. However, risk factors for mortality in patients with end-stage renal disease (ESRD), have yet to be delineated.

Current studies show that infection with SARS-CoV-2/COVID-19 has been associated with significant consequences in patients with chronic kidney disease [4-7]. Patients with end-stage renal disease (ESRD) undergo renal replacement therapy (RRT), dialysis, or renal transplant and often present with multiple underlying comorbidities, putting them at a greater risk of developing more severe forms of infection and higher mortality rates.

Unlike the general population, patients on dialysis cannot practice social distancing and other safety and preventative measures, due to their need for periodic

sessions and continuous treatment in hemodialysis units [12].

Recent research indicates that mortality rates in hemodialysis patients with COVID-19 are estimated to be approximately 20%, significantly higher compared to that of the general population [8-10]. These patients warrant complex management, as many treatment options that have been traditionally employed in the general population, have been avoided for the most part in patients with low glomerular filtration rate (GFR < 30 mL/minute) and on dialysis [11].

In light of these findings, as well as the lack of specific therapeutic options for COVID-19 for the time being, priority in vaccination programs, widespread and frequent testing, along with the standard of care therapy are the cornerstone of current management of COVID-19 in hemodialysis patients. In this context, determining strong and reliable predictors of severe disease and mortality is pivotal in implementing proactive treatment strategies and improving the long-term prognosis of hemodialysis patients with COVID-19 [13].

Methodology

Study design and objectives

The aim of this study was to investigate and determine potential risk factors, markers of disease severity, and mortality in patients with chronic kidney disease, receiving renal replacement therapy, and diagnosed with COVID-19.

We conducted an observational, retrospective, cohort study collecting data from the electronic medical records of a single dialysis center at Hygeia Hospital Tirana, Albania, between June 2020 to January 2022. A diagnosis of COVID-19 infection was established by positive RT-qPCR results in pharyngeal swabs.

Baseline patient characteristics, including demographic, clinical, laboratory data, relevant medical history, and underlying comorbidities were recorded. We obtained important laboratory findings including complete blood count (CBC), renal function tests (blood urea nitrogen and serum creatinine), proinflammatory markers (c-reactive protein, ferritin), and a coagulation panel with fibrin degradation products test (D-Dimer). This data was collected between the third and fifth day following a positive RT-PCR test.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics 26. Laboratory findings and comorbidities were scrutinized as risk factors for mortality. The group was split in vaccine availability, consisting of a full pre-vaccine group (June 2020 to June 2021) and post-vaccine group of vaccinated and non-vaccinated subjects (July 2021 to January 2022).

Patients were classified into three categories of severity: mild, moderate, and severe, in line with the classification proposed by the CDC. The mild disease was defined as the presence of symptoms of infection including fever, malaise, muscle pain, headache, sore throat, cough, loss of smell or taste, nausea, vomiting, and diarrhea, with no evidence of shortness of breath or low oxygen saturation on pulse oximetry. Patients were considered to have a moderate disease when they exhibited symptoms of infection along with shortness of breath and evidence of lower respiratory tract involvement but maintained oxygen saturation levels on pulse oximetry ≥ 94% on room air. Severe disease was defined as evidence of low respiratory tract involvement of more than 50% on imaging examinations, with severe shortness of breath, respiratory rate > 30 breaths/minute, and oxygen saturation levels by pulse oximetry < 94% on room air.

Receiver Operating Characteristic curve (ROC) analysis was conducted to determine the predictive value of elevated red blood cell distribution width (RDW) levels, eosinopenia, and lymphopenia and calculate the sensitivity, specificity, and their associated cut-off values, as well. Logistic regression analysis was conducted to identify possible independent risk factors of severe COVID-19 disease and the role of vaccines. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). All tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

Results

In this single-center study, among 170 hemodialysis patients, 52 were diagnosed with COVID-19 between June 2020 to June 2021. The median age was 63 years and 65.4% were men (Table 1). The prevalence of COVID-19 in our cohort was 30.5%, with an estimated mortality rate of 19.2%.

Based on their clinical and laboratory characteristics, patients were classified according to the disease severity (mild, moderate, severe). In our cohort, 40% of patients developed severe disease, while 35% and 25% presented with moderate and mild disease, respectively.

The most prevalent primary diseases leading to chronic kidney disease (CKD) requiring renal replacement therapy were diabetic nephropathy (32.7%), hypertensive nephrosclerosis (19.2%), glomerulonephritis (9.6%) and other disorders (38.5%).

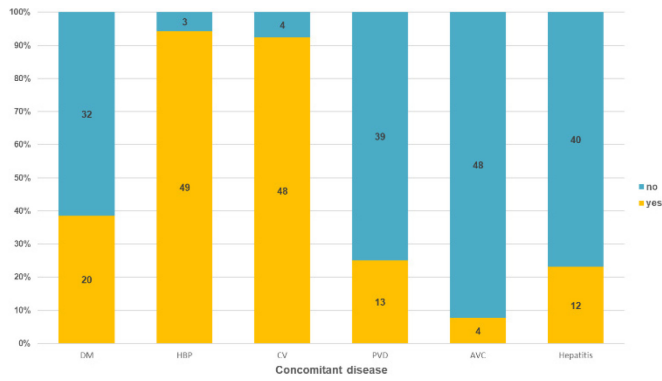**Figure 1.** Distribution of comorbidities in our study population.

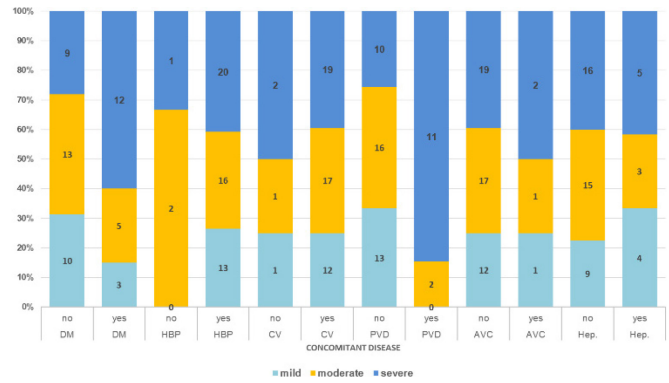**Figure 2.** Distribution of comorbidities according to their severity

Table 1. Baseline, clinical and laboratory data of the study population.

	N	Minimum	Maximum	Mean	± Std. Deviation
Age (years)	52	28	86	61.50	12.30
BMI (kg/m²)	50	17.70	35.30	25.30	3.80
UF (L/hr) Ultrafiltration Rate	47	2.00	5.00	3.10	0.80
WBC (µL)	47	2600	61700	8829.80	8607.30
LYM (%)	47	3.05	39.00	17.10	8.90
EO (%)	37	0.00	4.50	1.10	1.20
PLT (µL))	47	23000	338000	184957	74716
RDW (%)	47	11.10	20.40	14.50	2.20
CRP (mg/dL)	42	0.04	19.00	3.50	4.10
D-dimer (µ/mL)	11	0.20	8.49	3.00	2.90
Fe (ng/L)	38	56	2630	687.80	586.40

Table 2. ROC analysis for lymphopenia and eosinopenia as predictors of severity and mortality.

	AUC	Asymptotic 95% Confidence Interval		Positive if Greater Than orEqual To	Sensitivity	Specificity
		LowerBound	UpperBound			
EO % severity	0.79	0.63	0.94	0.31	0.74	0.64
LYM % severity	**0.82**	**0.69**	**0.96**	**15.70**	**0.79**	**0.78**
EO% exitus	0.81	0.61	1.00	0.18	0.73	0.75
LYM% exitus	**0.74**	**0.51**	**0.97**	**13.15**	**0.80**	**0.86**

Table 3. Mortality in the vaccinated and unvaccinated groups.

Variables in the equation		B	Wald	df	Sig.	Exp(B)	95% C.I Lower	EXP(B) Upper
Step 1b	Age	0.23	2.45	1	0.12	1.26	0.94	1.68
	Sex (1)	-23.37	0.00	1	1.00	0.00	0.00	
	Vaccination	-4.43	4.21	1	0.040	0.01	0.00	0.82
	Year in HD	-0.09	0.07	1	0.79	0.91	0.47	1.78
	Constant	-13.64	1.90	1	0.17	0.00		

Table 4. Disease severity in the vaccinated and unvaccinated groups.

Vaccination		Severity			Total
		Mild	Moderate	Severe	
NO	Count	1	1	4	6
	Vaccination Status	16.7%	16.7%	66.7%	100%
	Disease Severity	5.3%	14.3%	80%	19.4%
YES	Count	18	6	1	25
	Vaccination status	72%	24%	4%	100%
	Disease Severity	94.7%	85.7%	20%	80.6%
Total	Count	19	7	5	31
	Vaccination status	61.3%	22.6%	16.1%	100%
	Disease Severity	100%	100%	100%	100%

The most common, concomitant comorbidities in our cohort included high blood pressure, cardiovascular diseases, and diabetes mellitus (Figure 1).

The distribution of the underlying comorbidities according to their severity is presented below (Figure 2). Data showed that the mortality rate was higher in patients with diabetic nephropathy ($p < 0.04$) and peripheral vascular disease ($p < 0.01$).

Our analysis revealed that when comparing laboratory data between different levels of severity (mild, moderate, severe), lymphopenia ($p < 0.001$), eosinopenia ($p < 0.021$), high RDW ($p < 0.03$), high C-reactive protein ($p < 0.01$), high BMI ($p < 0.024$) and elevated serum ferritin ($p < 0.021$) levels, stood out as the most important risk factors for severe disease (Figure 3).

Moreover, ROC curves were used to evaluate the predictive value of these risk factors (Figure 4). Lymphopenia and eosinopenia were found to be the most significant predictors of mortality in hemodialysis patients with COVID-19 (Figure 5).

With regard to lymphopenia, cut-off values for severity and mortality were 15.70% and 13.15%, respectively, while for eosinopenia cut-off values for severity were 0.31% and for mortality was 0.18% (Table 2).

Between April 2021 to May 2021, hemodialysis patients were vaccinated. They were among the first patients to receive the vaccine, due to being considered a high-risk population. COVID-19 infections in the post-vaccination period were comprised of 80.6% of fully vaccinated patients (Pfizer BioNTech vaccine) and 19.4% of unvaccinated patients. The mortality rate among vaccinated patients was estimated to be 8%. On the other hand, the mortality rate in the unvaccinated population was found to be 66.7% ($p < 0.001$) (Table 3). After adjusting for age, sex, and the number of years receiving renal replacement therapy (hemodialysis), logistic regression analysis found the vaccination status to be statistically significant.

Figure 3. Risk factors for severe COVID-19 disease: (a) Correlation of lymphocyte count and disease severity. (b) Correlation of RDW and disease severity. (c) Correlation of CRP and disease severity. (d) Correlation of eosinophil count and disease severity.
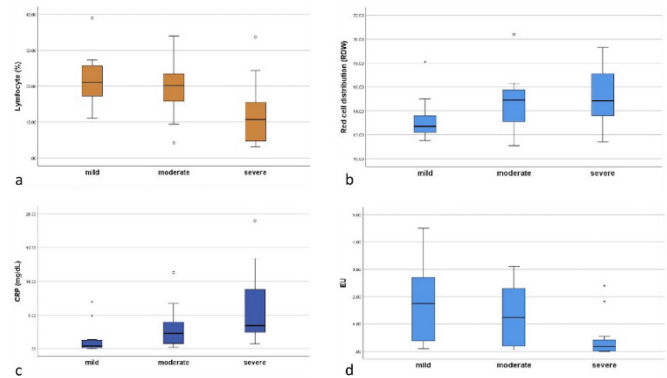
We investigated the severity of COVID-19 infection in the post-vaccination period. With respect to the vaccinated population, 72% of patients experienced mild symptoms, 24% had moderate symptoms and only 4% developed severe disease. Conversely, among unvaccinated patients, 80% developed severe disease, 14.3% had moderate disease and 5.3% experienced mild cases of COVID-19 infection ($p < 0.001$). After adjusting for age, sex, and the number of years receiving renal replacement therapy (hemodialysis), vaccination status ($p < 0.005$) and age ($p < 0.021$) were found to be statistically significant (Table 4).

Discussion

The COVID-19 pandemic has unevenly impacted patients with ESRD, who have been more prone to developing severe disease, due to their primary conditions, immunocompromised status, underlying comorbidities, and an inability to adhere to social distancing and other preventative measures, as opposed to the general population. The prevalence of infection with COVID-19 in our cohort was 30.5%. The mean age was 61.5 ± 2.3 years and 65.4% were men.

Figure 4. Predictors of disease severity: (a) Lymphopenia as a predictor of disease severity. (b) Eosinopenia as a predictor of disease severity.
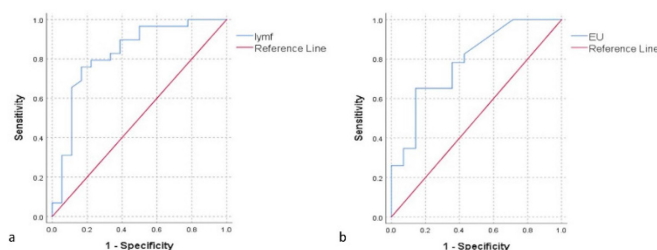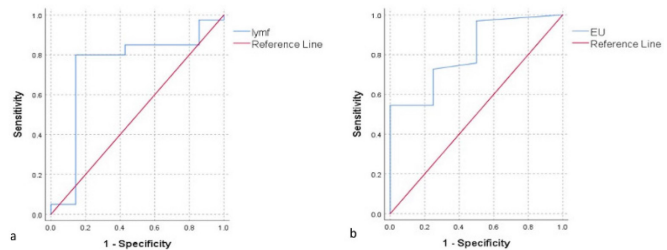

Figure 5. Predictors of mortality: (a) Lymphopenia as a predictor of mortality. (b) Eosinopenia as a predictor of mortality.

The mortality rate among hemodialysis patients in our study was 19.2%, consistent with findings from other larger studies [14,15]. The most common, pre-existing conditions in our cohort included high blood pressure, cardiovascular disease, and diabetes mellitus. The comorbidities associated with higher mortality rates in our study were diabetic nephropathy ($p < 0.04$) and peripheral vascular disease ($p < 0.01$).

Our analysis revealed elevated C-reactive protein ($p < 0.01$), high RDW ($p < 0.03$), lymphopenia ($p < 0.001$), and eosinopenia ($p < 0.021$), to be risk factors for severe disease.

RDW is a quantitative measurement of the variability of the volume and size of circulating red blood cells and elevated RDW has been found to be associated with adverse outcomes in numerous disorders including ischemic strokes, cerebral and pulmonary embolisms, heart failure, myocardial infarction, and carotid artery atherosclerosis [16-19]. Elevation in the RDW levels is associated with increased rates of red blood cell destruction or reduced lifespan and impaired erythropoiesis [17]. Studies suggest that infection with COVID-19 impacts red blood cell production and turnover either directly through premature destruction of peripheral red blood cells or their erythroid progenitors in the bone marrow, or indirectly due to hemolysis in the context of hemolytic anemia, coagulation disorders, as well as the activation of inflammatory cascades with upregulation of proinflammatory cytokines that suppress normal erythropoiesis [16]. Recently, several studies including our own, have highlighted the prognostic value of RDW in the severity of infection with COVID-19 [16-18]. Our study adds to the existing literature, potentially promoting an early risk stratification of patients, that is particularly valuable when treating vulnerable populations, such as hemodialysis patients.

Our study identified lymphopenia and eosinopenia as important predictors of disease severity and the most significant predictors of mortality, as well. Our analysis on lymphopenia conveyed that at a cut-off value of more than 15.70%, patients were expected not to develop severe disease in 79% of cases, whereas in terms of mortality, at a cut-off value of more than 13.15%, 80% of patients survived. Furthermore, regarding eosinopenia, we found that at a cut-off value of more than 0.31%, 74% of patients were expected not to develop severe COVID-19, while with respect to mortality, at a cut-off value of more than 0.18%, 73% of patients were expected to survive. These findings are corroborated by current research that has emphasized both lymphopenia and eosinopenia as key markers of severity and mortality [20-26].

Eosinophil levels have been a subject of study during the course of the pandemic, as multiple studies underscored the correlation between low eosinophil count and disease severity and questioned their role in SARS-CoV-2 infection [20-24]. Studies have postulated that eosinophils exert antiviral effects through the synthesis and secretion of peptides with antiviral properties (eosinophil-derived neurotoxin/eosinophil cationic protein) and acting as antigen presenting cells to CD8+ T lymphocytes [20-24]. A depletion of peripheral eosinophils either due to increased recruitment to respiratory tissue or inadequate production, may be associated with higher viral loads and severe disease [23,24].

Studies suggest that lymphopenia may arise due to the inflammatory cytokine storm that often develops in patients with severe COVID-19, the direct infection of T lymphocytes using the angiotensin-converting enzyme (ACE2), T-cell exhaustion, and impaired activation and expansion [25,26]. It has been consistently highlighted by multiple studies as a negative prognostic factor, associated with poor outcomes and high mortality [25-28].

In our study, we noted that elevated RDW, low eosinophil and lymphocyte counts in the acute phase of the infection, in admission, and persistently during the course of the infection were associated with a poor prognosis, lower rates of recovery, higher rates of disease severity and mortality.

Lastly, in terms of the impact of vaccination on severity and mortality rates, a remarkable difference was observed among the fully vaccinated and unvaccinated populations, with severity and mortality rates soaring in the unvaccinated group (80% and 66.7%, respectively), compared to the 4% severity and 8% mortality, in the vaccinated one.

Our study has several limitations worth noting. It is a small-scale study, owing to its single-center setting, as well as the significant reduction in the number of infected patients following the vaccine administration. Further studies with larger cohorts are necessary to better understand the underlying pathological mechanisms of severe COVID-19 disease, the risk factors for severe disease, and poor outcomes in patients with CKD and develop specific therapeutic options and treatment algorithms for these patients [27].

In mild and moderate disease supportive therapy was the standard of care. Antibiotic therapy was initiated in patients with confirmed secondary bacterial infections. In severe disease requiring oxygen

supplementation or ventilatory support, patients were started on dexamethasone 6 mg daily. Patients with critical disease with respiratory failure or multiple organ failure were managed in the ICU, using ARDS protocols. In our cohort, the use of antivirals and immunomodulators was avoided, due to the lack of official recommendations for dialysis patients. Moreover, there have been only a few small studies about the use of antivirals and immunomodulators in end-stage renal disease (ESRD) patients with an eGFR < 30 mL/minute/1.73 m^2 and notably, these medications have been used only in a few select patients, even in these studies. Due to the risk of potential thrombotic complications, we withheld Erythropoiesis-stimulating agents (ESA) during active infection unless hemoglobin levels fell below 8 g/dL in admitted patients and below 9 g/dL in outpatients, as recommended by current guidelines [30,31]. In these circumstances, patients were treated with one-half of the usual dose until full recovery, when the usual regimens were resumed.

Conclusions

Despite our acquired knowledge and experience in the past two years, COVID-19 and the emergence of new strains remain a serious challenge, particularly for susceptible populations like the chronically ill, including patients with chronic kidney disease. High RDW, low lymphocyte, and eosinophil counts, and elevated C-reactive protein (CRP), were found to be the most robust risk factors for severe COVID-19 disease. Lymphopenia and eosinopenia were revealed to be the most significant predictors of mortality. The mortality rate in our cohort was 19.2%. In the post-vaccination period, the mortality rate in the vaccinated population was 8%, whereas among unvaccinated patients was 66.7%, highlighting a significant difference between the two groups, associated with their vaccination status.

Incorporating prognostic predictors in management guidelines will enable a timelier risk-stratification model and early recognition of high-risk patients, ultimately providing a more personalized treatment approach, tailored to the specific needs of each patient, and improving the prognosis of COVID-19 infection in this vulnerable population.

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