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MORTALITY ANALYSIS IN CHRONIC DIALYSIS PATIENTS HOSPITALIZED WITH COVID-19: EXPERIENCE OF A COVID-19-ONLY NEPHROLOGY DEPARTMENT

Ileana Adela Văcăroiu[1,2], Cristiana David[1,2], Flavia Liliana Turcu[1,2], Anca Ioana Stănescu[2], Elena Cuiban[2], Andreea Ioana Pohariu[2], Andrei Angelescu[2], Filip Perde[4], Bogdan Florin Geavlete[1,3], Cosmin Victor Ene[1,3], Daniela Rădulescu[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy - Clinical Department no.3, "Sf. Ioan" Emergency Clinical Hospital, [2]Nephrology and Dialysis Department, [3]Urology Department, [4]"Mina Minovici" National Institute of Legal Medicine, Bucharest, Romania

Abstract: Limiting autopsies in deaths caused by COVID-19 reduced our ability to gain knowledge regarding many aspects of this lethal disease and also to answer potential medico-legal issues. Accordingly, it upraised the importance of the careful analysis of the clinical and biochemical determinants of the fatal evolution in SARS-CoV-2 infected patients. Maintenance dialysis patients, associating many comorbid conditions and an immunosuppressed status, are prone to a severe outcome of this disease. Since we were designated as a hospital dedicated exclusively to moderate/severe COVID-19 infections, we conducted an observational, single-center study in the Nephrology and Dialysis Department, aiming the analysis of mortality risk factors and determinants in maintenance hemodialysis patients admitted for this infection, which we discuss along with a focused review of the similar experiences in the last year's literature.

Keywords: COVID-19, maintenance hemodialysis patients, mortality.

INTRODUCTION

Analysis of the mortality causes is an important cornerstone in understanding the mechanisms of a disease. Limiting autopsies in deaths caused by COVID-19 reduced our ability to gain knowledge regarding many aspects of this lethal disease and also to answer potential medico-legal issues. Accordingly, it upraised the importance of the careful analysis of the clinical and biochemical determinants of the fatal evolution in SARS-CoV-2 infected patients.

As we learned from many meta-analysis, in patients with COVID-19 the presence of comorbidities is associated with higher risks of severe complications and death [1,2]. Chronic kidney disease (CKD) patients are a special category in this regard, cumulating many other conditions that can worsen the course of the disease (diabetes mellitus, hypertension, coronary heart disease, cardiac insufficiency etc.) [3,4]. Reports of the transmission of COVID-19 infection among maintenance hemodialysis (MHD) patients are heterogeneous and the present literature data cannot offer accurate information on the incidence or clinical course of the disease in this population [5-7]. Some early trials, exposing the experiences in Wuhan, China and Brescia, Italy, concluded that MHD patients had less severe infection forms compared to general populations and even to transplanted patients [6,8]. On contrary, the most recent experiences showed that mortality rates for MHD patients were the same or even higher that in non-renal population, varying between 27-41% [9-13] and reaching 50% in some studies [14,15]. These discrepancies and the recrudescence of the disease in the third wave with the viral modifications brought by the new strains, emphasized the importance of further studies and determined us to expose our experience as a COVID-19-dedicated Nephrology Department in an emergency hospital.

Aims

To evaluate the clinical and biochemical characteristics, correlated with the disease course,

*Correspondence to: Lecturer Cristiana DAVID, Nephrology and Dialysis Department, „Sf. Ioan" Emergency Clinical Hospital, 13 Vitan-Barzesti Avenue, Bucharest, 042122, Romania. E-mail: cristianadavid@yahoo.com

and outcomes in MHP admitted with severe and critical forms of COVID-19. We conducted an analysis of mortality risk factors and determinants in these patients, along with an extended review of the experiences presented in the last year's literature.

MATERIAL AND METHODS

Since November 2020 our hospital was designated to treat only patients with severe and critical SARS-CoV-2 infections, thereupon in the next 4 months our Nephrology and Dialysis department admitted 167 COVID-19-positive CKD patients; 77 were MHD patients from 9 dialysis centers in the region. We conducted a retrospective, observational study including all the RT-PCR-confirmed SARS-CoV-2 infected MHD patients admitted in our department during a 4-month interval; due to the impossibility to obtain all the data needed for the study, patients who died within the first 24 hours of hospitalization were excluded (Fig. 1).

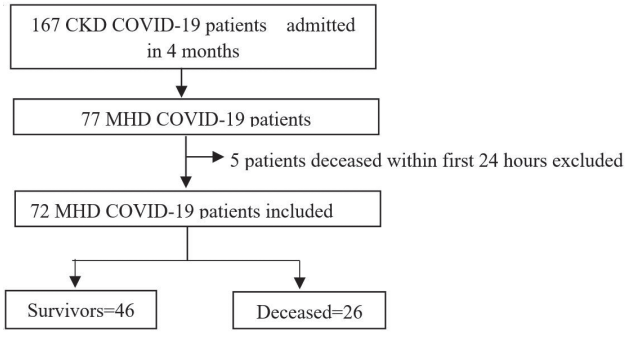

Figure 1. Study design.

After obtaining the approval of the Local Ethical Committee of the Hospital (no 4925/March 2021), the demographic characteristics, admission and discharge clinical and laboratory data were collected from electronic medical records, including: disease severity and oxygen supplementation need, etiology of chronic kidney disease (CKD), comorbidities, laboratory tests (hemoglobin, leukocyte, lymphocyte and platelet counts, serum albumin, ferritin, C-reactive protein (CRP), procalcitonine, IL-6 (interleukin-6), lactate dehydrogenase, D-dimers, liver function tests), used medication, complications, length of hospitalization and the status at discharge.

The COVID-19 severity was assessed by the infectious disease specialist at admission, according to guidelines [16], along with the specific COVID-19 treatment regimen. Only severe cases or those with potentially severe evolution were allocated to our department. Periodical re-assessments by the infectious disease physician established the dynamic treatment regimen, adapted to the dialysis schedule and the disease course. We noted the cause of death according to the death certificate stated by the attending physician and approved by the pathologist. Acute Respiratory Distress Syndrome (ARDS) was diagnosed according to the 2012 Berlin criteria and Multiple Organ Dysfunction Syndrome (MODS) was established using SOFA score [17,18].

Statistical analysis used IBM SPSS Statistics 25 and Microsoft Office Excel/Word 2013. The quantitative variables were tested for distribution using the Shapiro-Wilk test and expressed as mean with standard deviation or median with interquartile range (IQR). For independent quantitative variables with nonparametric distribution we used the Mann-Whitney U test, and for the independent quantitative variables with parametric distribution the Student test was used. Qualitative variables were expressed as absolute values or percentages, and tested with Fisher/Pearson Chi-Square tests. The Z-test and Bonferroni correction detailed the results in contingency tables. Multivariate Cox regression method was used for assessing the effects upon the risk of death.

RESULTS

72 patients were included in our study. The detailed baseline characteristics are as follows: the median age in the studied population was 64.51 ± 12.29 years and the most representative categories were the 41-65 and 66-80 age groups accounting for 44.4% respectively 41.7% of the patients. The majority of the patients were men (65.3%). The most common comorbidities were represented by hypertension (97.2%), obesity (54.4%), coronary heart disease (43.1%), atherosclerosis (38.9%), diabetes mellitus (37.5%), followed by pulmonary disease (16.7%) and malignancies (15.3%). We've observed that the most frequent CKD etiologies were represented by diabetic nephropathy (35.6%) and hypertensive nephropathy (25.4%). Oxygen therapy was required in 66 patients during hospitalization (91.66%); endotracheal intubation (ETI) and mechanical ventilation was needed in 17 patients (23.6%). Out of the 38.9% of patients with infectious complications, 19.4% were identified with sepsis and 8.3% with Clostridium difficile colitis. The germs involved were Enterococcus spp (8 patients), Acinetobacter spp (6 patients) and Klebsiella spp

(5 cases). 30.6% of patients developed hemorrhagic complications; among them, 40.9% presented with soft tissue hematomas. We identified thrombosis in 5.6% of our patients (pulmonary embolism, arteriovenous fistula thrombosis). Hospitalization criteria for MHD SARS-CoV-2-infected patients were either severe/critical forms of COVID infection (64 cases), or mild/moderate COVID-infection associated with potential severe evolution (advanced age, comorbid conditions: malignancies, diabetes, etc). The median of the hospital length stay was 15 days (IQR=13-19 days), and the recorded mortality rate was 36.1% (Table 1).

Laboratory test analysis showed that 18.1% of the patients had leukocytosis and 73.6% presented with lymphopenia. A mean Hb of 9.99 ± 2.046 g/dL was noted and the median of the albumin value qualified as normal.

Table 1. Clinical characteristics and biological features of the patients included in the study

Parameter (N=72)	**Value**
Sex (Nr. (%))	25 (34.7%) F, 47 (65.3%) M
Age (Median ± SD) (years)	64.51 ± 12.29 (p=0.328*)
Age groups (No. (%))	
< 41	3 (4.2%)
41-65	32 (44.4%)
66-80	30 (41.7%)
> 80	7 (9.7%)
Obesity (No. (%)) (N=57)	26 (45.6%) - , 31 (54.4%) +
Coronary heart disease (Nr. (%))	41 (56.9%) - , 31 (43.1%) +
Atherosclerosis (No. (%))	44 (61.1%) - , 28 (38.9%) +
Malignancy (No. (%))	61 (84.7%) -, 11 (15.3%) +
Pulmonary disease (No. (%))	60 (83.3%) -, 12 (16.7%) +
Diabetus mellitus (No. (%))	45 (62.5%) -, 27 (37.5%) +
CKD Etiology (No. (%)) (N=59)	
Tubulointerstitial nephropaties	43 (72,85) -, 16 (27,15%) +
Glomerular nephropaties	54 (91,52%) -, 5 (8,48%) +
Multiple myeloma	57 (96,61%) -, 2 (3,39%) +
Diabetic nephropathy	38 (64,4%) -, 21 (35,6%) +
Hypertensive nephropathy	44 (74,58%) -, 15 (25,42%) +
Oxygen therapy (No.(%))	6 (8.3%) - , 66 (91.6%) +
Infectious complications (No. (%))	44 (61.1%) - , 28 (38.9%) +
Sepsis	58 (80.6%) -, 14 (19.4%) +
Clostridium difficile colitis	66 (91.7%) -, 6 (8.3%) +
Other infections	63 (87.5%) -, 9 (12.5%) +
Hemorrhages (No. (%))	50 (69.4%) - , 22 (30.6%) +
Hematomas (No. (%))	63 (87.5%) -, 9 (12.5%) +
Thrombosis (No. (%))	68 (94.4%) - , 4 (5.6%) +
Death (No. (%))	46 (63.9%) -, 26 (36.1%) +
Length of hospital stay (Median (IQR)) (days)	15 (13-19) (**p=0.005***)
White blood cells (Median (IQR)) (No./µL)	6995 (4545-9910) (**p<0.001***)
Leukocytosis (No. (%))	59 (81.9%) -, 13 (18.1%) +
Lymphocytes (Median (IQR)) (No./µL)	645 (397.5-1022.5) (**p<0.001***)
Lymphopenia (No. (%))	19 (26.4%) - , 53 (73.6%) +
Hb (Mean ± SD) (g/dL)	9.99 ± 2.046 (p=0.545*)
Albumin (Median (IQR)) (g/dL) (N=68)	3.715 (3.357-4) (**p=0.007***)
D-dimer (Median (IQR)) (µg/mL)	1.52 (0.85-2.645) (**p<0.001***)
Ferritin (Median (IQR)) (ng/mL) (N=57)	1235 (745.6-2348.5) (**p<0.001***)
IL-6 (Median (IQR)) (pg/mL) (N=45)	50.79 (19.88-106.3) (**p<0.001***)
CRP (Median (IQR)) (mg/dL) (N=71)	90.51 (29.39-146.9) (**p<0.001***)
Procalcitonine (Median (IQR)) (ng/mL) (N=54)	0.79 (0.41-2.955) (**p<0.001***)
ESR (Median (IQR)) (mm/h) (N=70)	82.5 (53.5-99.25) (**p=0.013***)
aPTT (Median (IQR)) (s) (N=71)	33.3 (29.8-37.9) (**p<0.001***)
INR (Median (IQR))	1.07 (1-1.2) (**p<0.001***)
Specific treatment (No. (%))	30 (41.7%) - , 42 (58.3%) +
Remdesivir/Veklury	57 (79.2) - , 15 (20.8%) +
Tocilizumab/Roactemra	58 (80.6%) - , 14 (19.4%) +
Anakinra/Kineret	40 (55.6%) - , 32 (44.4%) +

The inflammatory tests were profoundly altered in all of our patients, with median values highly elevated for ESR, D-dimers, ferritin, IL-6, CRP and procalcitonine; the coagulation tests were within normal range. We administered antiviral and immunomodulatory therapy in 58.3% of our patients: 20.8% received Remdesivir, 19.4% received Tocilizumab and 44.4% Anakinra. However, our study was not powered to assess the predictive value of any treatment and we could not illustrate any connection between these therapies and the risk of mortality because medications were prescribed based on the guidelines that were permanently updated.

The characteristics of the patients in the discharged group were compared to those in the non-survivors group (Table 2). There were no differences between groups regarding the sex ratio or the association of some comorbidities: obesity, diabetes mellitus, atherosclerosis, malignancies and previous pulmonary diseases. The majority of the patients in the 41-65 years age group were survivors, whilst the percentage of deaths in the >81 years group was significantly higher. Coronary heart disease was identified in the majority of the deceased patients. The differences were significant regarding the CKD etiology, with a higher rate of survival in patients with tubulointerstitial nephropathies.

There were no differences regarding the prevalence of most complications (Clostridium colitis, hemorrhages, hematomas and thrombosis) between the two groups, excepting sepsis, which was mostly identified in non-survivors. Laboratory tests abnormalities at admission associated with greater mortality were leukocytosis, hypoalbuminemia, increased values of ferritin, IL-6 and CRP. There were no notable differences between the two studied groups regarding hemoglobin levels, severity of lymphopenia, ESR, INR, aPTT, D-dimers and procalcitonine values. The median length of hospitalization was similar in the two groups.

In the multivariate analysis, sepsis was the strongest risk factor for death, increasing the death risk by 3.532 fold (95% CI: 1.277-9.772). Most of these patients had high leukocyte count at admission, but without sepsis criteria (sepsis was developed during hospitalization). The death risk was also significantly higher in patients with old age, coronary heart disease and high ferritin levels (Table 3).

DISCUSSION

Few studies approach the fatal outcome and its determinants in COVID-19 patients undergoing chronic dialysis. Given the recommendation to limit autopsy in these patients, the results of the studies are dissenting, depending on the design of the trial, the severity of the disease forms included, the specifics of the performing unit (mostly dialysis centers). Early COVID-19 reports mentioned diabetes mellitus, hypertension, cardiovascular diseases, advanced age, male sex and active malignancy, among the most important risk factors for severe disease and increased mortality due to SARS-CoV-2 infection, without mentioning CKD, despite the previous knowledge that CKD is an important risk factor for severity in bacterial and viral infections [9,18,19]. Later reports highlighted that CKD was one of the most prevalent risk factor for severe COVID-19 [9,19,20].

We performed a retrospective analysis of the outcome for mostly severe/critical COVID-19 cases in MHD patients. The mortality rate in our study was 36.1%, lower than in some studies [14,15], but higher than in trials performed in singular dialysis centers or departments in which all the cases were enrolled – asymptomatic, mild and severe [9,10]. The outcome was the poorest among patients needing mechanical ventilation; 16 from 17 cases died. This result is in line with other reports.[10].

Among the patients who died, the cause of death was respiratory failure secondary to ARDS in 15 of 24 cases (63%), bacterial sepsis with septic shock in 4 cases, MODS in 2 patients and sudden death due to cardiovascular causes in 3 patients.

In contrast to studies reporting a higher rate of mortality in men, we have found no such correlation in our cohort; male gender prevailed in both groups [21,22]. The non-survivors were significantly of older age (70.46 ± 11.473 years), with patients aged 80 and above most often non-survivors (23.1% *vs.* 2.2%, p=0.004) and patients aged between 66 and 81 accounting for 73% of the deaths. Old age is associated with a pro-inflammatory and pro-coagulant condition termed "inflammaging" providing an explanation for the strong correlation between advanced age and COVID-19 mortality in the general population [18]. Additionally, MHD population is exposed to various factors inducing themselves premature senescence: oxidative stress, chronic retention of uremic toxins, and alteration on gut microbiome [22].

Among MHD patients, classical risk factors for COVID-19 morbidity and mortality do not have the same impact as in the general population. Thus diabetes, hypertension, malignancy, chronic pulmonary diseases do not appear to increase the risk of death in chronic

Table 2. Comparison of the analyzed data in relation to survival

Parameter	Survivors	Non-survivors	P
Sex (No. (%))	17 (37%) F, 29 (63%) M	8 (30.8%) F, 18 (69.2%) M	0.797*
Age (Mean ± SD) (years)	61.15 ± 11.541 (p=0.175**)	70.46 ± 11.473 (p=0.240**)	**0.002*****
Age groups (No. (%))			
< 41	3 (6.5%)	0 (0%)	
41-65	**25 (54.3%)**	**7 (26.9%)**	**0.004***
66-80	17 (37%)	13 (50%)	
> 80	**1 (2.2%)**	**6 (23.1%)**	
Obesity (No. (%))	18 (47.4%) -, 20 (52.6%) +	8 (42.1%) - , 11 (57.9%) +	0.782*
Coronary heart disease (No. (%))	31 (67.4%) - , 15 (32.6%)+	10 (38.5%) - , 16 (61.5%) +	**0.026***
Atherosclerosis (No. (%))	31 (67.4%) - , 15 (32.6%)+	13 (50%) - , 13 (50%) +	0.208*
Malignancies (No. (%))	41 (89.1%) - , 5 (10.9%) +	20 (76.9%) - , 6 (23.1%) +	0.188*
Pulmonary disease (No. (%))	39 (84.8%) - , 7 (15.2%) +	21 (80.8%) - , 5 (19.2%) +	0.746*
Diabetes mellitus (No. (%))	30 (65.2%) - , 16 (34.8%)+	15 (57.7%) - , 11 (42.3%) +	0.615*
CKD etiology (No. (%))			
Tubulointerstitial nephropaties	**15 (35.7%)**	**1 (5.9%)**	
Glomerular nephropaties	3 (7.1%)	2 (11.8%)	
Multiple myeloma	**0 (0%)**	**2 (11.8%)**	**0.028***
Diabetic nephropathy	13 (31%)	8 (47.1%)	
Hypertensive nephropathy	11 (26.2%)	4 (23.5%)	
Infectious complications (No. (%))	35 (76.1%) - , 11 (23.9%)+	9 (34.6%) - , 17 (65.4%) +	**0.001***
Sepsis	44 (95.7%) - , 2 (4.3%) +	14 (53.8%) - , 12 (46.2%) +	**<0.001***
Clostridium difficile colitis	41 (89.1%) - , 5 (10.9%) +	25 (96.2%) - , 1 (3.8%) +	0.408*
Other infections	42 (91.3%) - , 4 (8.7%) +	21 (80.8%) - , 5 (19.2%) +	0.269*
(No. (%))	31 (67.4%) - , 15 (32.6%)+	19 (73.1%) - , 7 (26.9%) +	0.791*
Hemorrhages (No. (%))	42 (91.3%) - , 4 (8.7%) +	21 (80.8%) - , 5 (19.2%) +	0.269*
Thrombosis (No. (%))	45 (97.8%) - , 1 (2.2%) +	23 (88.5%) - , 3 (11.5%) +	0.131*
Length of hospital stay (Median (IQR)) (days)	15 (13-20) (**p=0.003****)	15 (8-17.5) (p=0.214**)	0.309*****
Leukocytes (Media (IQR)) (No./µL)	5735 (3905-9135) (**p<0.001****)	8645 (6552.5-12342.5) (**p<0.001****)	**0.003*****
Leukocytosis (No. (%))	41 (89.1%) - , 5(10.9%) +	18 (69.2%) - , 8 (30.8%) +	**0.035******
Lymphocytes (Median (IQR)) (No./µL)	735 (412.5-1112.5) (**p=0.013****)	570 (377.5-835) (**p<0.001****)	0.185*****
Lymphopenia (No. (%))	15 (32.6%) - , 31 (67.4%)+	4 (15.4%) - , 22 (84.6%) +	0.165*
Hb (Mean ± SD) (g/dL)	9.854 ± 1.838 (p=0.656**)	10.231 ± 2.389 (p=0.481**)	0.457***
Albumin (Median (IQR)) (g/dL) (N=68)	3.86 (3.445-4.045) (**p<0.001****)	3.47 (3.09-3.8) (p=0.746)	**0.041*****
D-dimer (Median (IQR)) (µg/mL)	1.52 (0.91-2.692) (**p<0.001****)	1.715 (0.797-2.355) (**p<0.001****)	0.870*****
Ferritin (Median (IQR)) (ng/mL) (N=57)	1007.9 (541.8-1751.5) (**p<0.001****)	2079 (1197-3756) (**p<0.001****)	**0.001*****
IL-6 (Median (IQR)) (pg/mL) (N=45)	34.09 (11.71-71.61) (**p<0.001****)	101.51 (48.41-626.92) (**p<0.001****)	**0.002*****
CRP (Median (IQR)) (mg/dL) (N=71)	46.32 (18.71-141.2) (**p<0.001****)	113.235 (58.837-167.137) (**p=0.001****)	**0.029*****
Procalcitonine (Median (IQR)) (ng/mL) (N=54)	0.76 (0.375-2.985) (**p<0.001****)	1.6 (0.525-4.115) (**p<0.001****)	0.199*****
ESR (Median (IQR)) (mm/h) (N=70)	75.16 ± 29.637 (p=0.114**)	79.54 ± 32.398 (p=0.082**)	0.566**
aPTT (Median (IQR)) (s) (N=71)	33.4 (29.85-40.05) (**p<0.001****)	32.8 (27.9-36.175) (**p<0.001****)	0.531*****
INR (Median (IQR))	1.055 (0.995-1.1725) (**p<0.001****)	1.115 (1.015-1.29) (**p<0.001****)	0.152*****
Specific treatment (No. (%))	20 (43.5%) - , 26 (56.5%)+	10 (38.5%) - , 16 (61.5%) +	0.805*

*Fisher's Exact Test, **Shapiro-Wilk Test, ***Student T-Test, ****Mann-Whitney U Test, *****Pearson Chi-Square Test.

Table 3. The analysis of risk factors associated with the mortality rate

Parameter	Univariate analysis (HR – 95% CI)	Multivariate analysis (HR – 95% CI)
Age	1.044 (1.005-1.084) (**p=0.027**)	1.014 (0.973-1.056) (p=0.507)
CHD	2.28 (1.032-5.038) (**p=0.042**)	1.361 (0.490-3.782) (p=0.554)
Infectious complications	1.774 (0.779-4.041) (p=0.172)	-
Sepsis	2.777 (1.277-6.037) (**p=0.010**)	3.532 (1.277-9.772) (**p=0.015**)
Leukocytes	1.000 (1.000-1.000) (p=0.122)	-
Leukocytosis	2.093 (0.906-4.831) (p=0.084)	-
Albumin	0.705 (0.378-1.313) (p=0.270)	-
Ferritin (/100)	1.005 (1.001-1.008) (**p=0.006**)	1.003 (0.999-1.006) (p=0.133)
IL-6	1.001 (1.000-1.001) (p=0.177)	-
CRP	1.004 (1.000-1.007) (p=0.065)	-

dialysis population, but there is evidence that history of ischemic heart disease increases mortality [9,24-26]. Malignancies are shown to increase the risk of acute kidney injury, especially in some types of tumors [27]. Obesity might worsen the clinical course of COVID-19 by decreasing expiratory reserve volume, diaphragm excursion, and restricting ventilation. Abdominal obesity increases inflammatory cytokines and oxidative stress [28].

In our trial, obesity was not a risk factor for mortality, given the fact that obesity was prevalent in both groups; the same observation was noted regarding atherosclerosis, malignancies, pulmonary disease or diabetes mellitus in our trial – they had no influence upon the mortality risk. In contrast, the outcome of death was more frequent in patients with coronary heart disease (61.5% *vs*. 32.6%, p=0.026). There are other studies reporting that the influence of coronary disease on COVID-19 mortality risk is more important than the presence of pre-existing chronic obstructive pulmonary disease [29-31].

Regarding the primary kidney disease association with the mortality risk, the Z tests with Bonferroni correction revealed that patients with tubulointerstitial nephropathies had significantly higher survival rates compared to patients with other CKD etiologies (35.7% *vs*. 5.9%), in contrast with the lack of influence found in another recent study [30].

Infections are the second most common cause of death for patients on dialysis, some studies finding a several-hundred-fold higher annual mortality rate secondary to sepsis as compared to that in the general population [8,31]. In our study, Clostridium difficile colitis and other infections were not found to increase the risk of death (p=0.269), but sepsis was strongly associated with greater mortality (46.2%, p<0.001); this group had a significantly higher value of the leukocyte count at admission, but no higher procalcitonine levels. The procalcitonine levels were observed to increase later in the course of the hospitalization, along with the sepsis onset.

SARS-CoV-2-induced ischemic organ damage appears to be associated with a hyper inflammatory state, cytokine storm, vascular endothelial damage or fibrinogen consumption coagulopathy. Viral pathogens activate the innate immune system, leading to the production of pro-inflammatory cytokines. Further activation of the innate immune response to eradicate the virus induces overproduction of pro-inflammatory cytokines, resulting in a "cytokine storm". These molecules activate the endothelial cells, leading to endothelial dysfunction and initiating the coagulation cascade [32-37]. Although we registered a high frequency of vascular complications, we have found no correlation between the occurrence of hemorrhages (p=0.791), hematomas (p=0.074) or thrombosis (p=0.131) and the risk of mortality. The same lack of influence was noted regarding the hemoglobin values and the coagulation tests.

The impact of hypoalbuminemia on mortality in hospitalized SARS-CoV-2 patients has been previously reported in the general population. In our study, the non-survivors had substantially lower levels of albumin. It can be related to the malnutrition-inflammation complex syndrome, which is an important risk factor for cardiovascular mortality [30].

In SARS-CoV-2 infection, cytokines exert their pathogenic effects through various mechanisms. The most important one, IL-6, can increase vascular permeability and promote the secretion of pro-inflammatory cytokines by endothelial cells themselves, thereby amplifying the cytokine release [38]. IL-6 stimulates production of CRP [39]. In addition, the activation of the monocyte-macrophage system, which is a vital part of the inflammatory storm, stimulates ferritin production [40]. We have noted significantly higher values of ferritin (p=0.001), IL-6 (p=0.002), CRP (p=0.029) in the non-survivor group. On the contrary,

elevated D-dimers were not associated with greater mortality in our study. D-dimer levels are not reliable predictors of mortality in MHD patients, as elevated levels have also been described in stable conditions [41].

There were no marked differences between the survivors and the non-survivors regarding the length of hospital stay (p=0.309). In many cases, the period of time between the admission and death was short, stressing out the severe forms of the SARS-COV-2 infections at admission.

There are some limitations in our study. Most importantly, we could not assess the influence of the antiviral/immunomodulatory medication in this group of patients, as the prescription rules were repeatedly changed due to modifications in guidelines. Secondly, the relative small number of patients; unfortunately, the analysis can be continued in the coming months, as the pandemic is far from being overcome.

In conclusion, the MHD patients with severe and critical forms of COVID-19 enrolled in our study had a high mortality rate, greater than the one observed in outpatient dialysis centers, with sepsis as the strongest risk factor for death, followed by old age, the presence of coronary heart disease and high ferritin levels at admission.

Conflict of interest

The authors declare that they have no conflict of interest.

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