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Retrospective Cohort Study

Clinical presentation and outcomes of chronic dialysis patients with coronavirus 19 disease: A single center experience from Greece

Bacharaki D *et al*. Hemodialysis patients with COVID-19 in Greece

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is still a menacing pandemic, especially in vulnerable patients. Morbidity and mortality from COVID-19 in maintenance hemodialysis patients (MHD) patients is considered worse than the general population, but varies across continents and countries in Europe.

AIM

To describe the clinical course and outcomes of hospitalized MHD with COVID-19 in a retrospective observational single center study in Greece.

METHODS

We correlated clinical, laboratory and radiological data with the clinical outcomes of MHD patients hospitalized with COVID-19 during the pandemic. The diagnosis was confirmed by real-time polymerase chain reaction. Outcome was determined as survivors *vs* non-survivors and "progressors" (those requiring oxygen supplementation because of COVID-19 pneumonia worsening) *vs* "non- progressors".

RESULTS

We studied 32 patients (17 males), with a median age of 75.5 years (IQR 58.5-82) old. Of those, 12 were diagnosed upon screening and 20 with related symptoms. According to the World Health Organization (WHO) score the severity on admission was mild disease in 16, moderate in 13 and severe in 3 cases. Chest computed tomography (CT) showed 1-10% infiltrates in 24 patients. Thirteen "progressors" were recorded among included patients. The case fatality rate was 5/32 (15.6%). Three deaths occurred among "progressors" and two in "non-progressors", irrespective of co-morbidities and gender. Predictors of mortality on admission included frailty index, chest CT findings, WHO severity score and thereafter the increasing values of serum LDH, d-dimers and decreasing serum albumin. Predictors of becoming a "progressor" included increasing number of neutrophils and neutrophils/Lymphocytes ratio.

CONCLUSION

Patients on MHD seem to be at higher risk of COVID-19 mortality, distinct from the general population. Certain laboratory parameters on admission and during the follow up may be helpful in risk stratification and management of patients.

Key Words: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Dialysis; Greece; Clinical course; Outcome

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Core Tip: Maintenance hemodialysis patients, a group of patients with presumed high mortality, have been reported to experience worse outcomes of coronavirus disease 2019 (COVID-19), compared to the general population internationally. However, there is a considerable variation in the reported rates of disease remission and death between different continents and countries. In this article we present the outcomes of thirty two patients in chronic dialysis who became positive for COVID-19 in the era before vaccines became available.

INTRODUCTION

Background/rationale

Nearly two years have elapsed after the pronouncement of the novel coronavirus disease 2019 (COVID-19), on March 11, 2020 by the World Health Organization (WHO) as a global pandemic, following its first recognition in Wuhan, China, in December 2019[1]. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is manifested in the majority of cases with symptoms related to the upper respiratory system or with development of mild pneumonia in 81% of cases[2]. Only 15% of infected patients develop severe lung disease, requiring oxygen support, while 5% of them progress to critical disease with complications, such as respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and multiorgan failure[3-4]. A dysfunctional as opposed to a healthy host immune response is supposed to play an important role for the final outcome[5]. Patients prone to the severe form of the disease are considered to be elderly, and those with co-morbidities including diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, obesity[6-7] and chronic kidney disease, although at first not included[8]. Regarding patients with end-stage kidney disease (ESKD), who are

maintained with hemodialysis or peritoneal dialysis, results from the ERACODA collaboration (the European database collecting clinical information of patients on kidney replacement therapy with COVID-19) revealed some peculiarities compared to the general population, i.e. prevalent co-morbidities like hypertension, diabetes mellitus, coronary artery disease, heart failure and chronic lung disease did not emerge as independent risk factors for mortality[6]. Notably, the aforementioned co-morbidities are highly prevalent in patients with chronic kidney disease, which is itself considered by default, an independent risk factor for increased cardiovascular and all-cause mortality[9-10]. Yet, some studies have reported increased mortality in ESKD patients with COVID-19[11-12], where others have concluded that these patients are somehow being "protected" from the severe form of COVID-19[13-14]. The reported death rates vary substantially across countries[15] and thus, genetic factors have been implicated to play a role in the development of the severe form of the disease[16].

Objectives

A cohort of patients with COVID-19 and ESKD on dialysis, who were admitted in our hospital during pandemic, was studied, attempting to identify potential differences in terms of the clinical presentation and outcome of COVID-19 compared to the general population. We also searched for distinctive features, clinical, radiological, or laboratory that could serve as predictors in order to recognize patients in high risk for COVID-19 adverse outcome.

MATERIALS AND METHODS

Study Design

This is an observational, analytical, retrospective cohort study which took place in a single center from Greece. It was approved by the Scientific Committee of the Hospital.

Setting

The study included MHD patients, who were admitted in our hospital from April 23 2020 till February 3, 2021 and were followed until death or release from hospital. All data were retrospectively collected from patients' electronic records and medical charts and included demographics, clinical features, laboratory and radiological data, treatment schemes, clinical course and outcome.

Participants

All included patients had signed informed consent and were ≥ 18 years old, had COVID-19 confirmed by polymerase chain reaction (PCR) test within the last 5 d prior to admission and were on MHD for more than 3 mo. Exclusion criteria were patients with COVID-19 with acute kidney injury undergoing temporary hemodialysis, MHD patients who were hospitalized with other types of pneumonia (non-related to SARS-CoV-2), active cancer or autoimmunity. The PCR test was performed either because of symptoms, which might be attributed to COVID-19, or in case of a history of exposure to an infected patient or working personnel, or as a regular routine screening test.

Variables

Diagnosis of COVID-19 was confirmed by positive throat- swab specimens for SARS-CoV-2 using the PCR methodology, as has been described[17]. Symptoms, if present, were recorded.

Regarding clinical presentation, each patient was classified at the time of admission, according to the classification of WHO for COVID-19 severity (mild, moderate, severe and critical disease) as described[4]. Accordingly, the disease was characterized as mild if there was absence of pneumonia or hypoxia, moderate if there were clinical signs of pneumonia with oxygen saturation (SatO2) > 90% and as severe if the patient had one or more of the following: respiratory rate > 30/min, respiratory distress or SatO2 < 90%. The disease was determined as critical disease in case of acute respiratory distress syndrome, sepsis or septic shock (Supplementary Table 1). In addition, at the time of

admission, all patients were scored for their status of frailty, using the 9-point frailty scale, as previously described[18].

Regarding the clinical course, patients were grouped based on worsening or not of COVID-19 pneumonia, as follows: Those who required oxygen supplementation (for the first time, or amplification of previous) because of worsening of COVID-19 pneumonia at the time of admission, at discharge or before death, were categorized as "progressors", while those who remained in stable clinical condition, were categorized as "non-progressors" or "stable".

Regarding the final outcome (death or release from hospital), patients were grouped into a survival group and a non-survival (deceased) group. In case of death, the precise cause was recorded and characterized as COVID-19 related or not. The case fatality rate (CFR) was calculated according to previous reports[19]: The number of deaths attributed to the disease were divided by the number of diagnosed cases and multiplied by 100. Since causes of death in COVID-19 patients have been reported to differ between MHD patients and the general population[12], we recorded the CFR as the total number of deaths in COVID-19 patients but also distinguished COVID-19 related deaths attributed to respiratory failure from SARS-CoV-2 pneumonia *vs* non-related to COVID-19, *i.e.* attributed to other causes, in patients with no respiratory worsening.

Data sources/ measurement

Information regarding the past medical history of patients was recorded from their medical charts including the presence of all comorbidities such as hypertension, diabetes mellitus, coronary artery disease, heart failure and chronic lung disease.

Laboratory data: Routine blood examinations included complete blood count, coagulation profile, inflammatory markers *i.e.* c-reactive protein (CRP) and ferritin, and serum biochemistry (renal and liver function and albumin). The data were recorded from the day of admission till death or release from hospital. Thus, we had the opportunity to study the kinetics of certain laboratory parameters that have emerged as

prognostic markers in the general population[20] including neutrophils to lymphocytes Ratio (NLR), lymphocytes, lactate dehydrogenase) (LDH), CRP, ferritin, Il-6, d- dimers, troponin, albumin, white blood cells (WBC). Specifically, we recorded the maximal value (or lowest in parameters such as albumin) in the time interval between admission and 10th-day and calculated the increase as a percentage from admission to the highest (or lowest) value of 10 d by dividing this difference with the value at admission.

Radiology data: All patients with COVID-19 underwent a computed tomography (CT) of the chest on admission, as per hospital protocol for COVID-19. All CT scans performed in COVID-19 patients were conducted using a Philips Brilliance™ 64 CT scanner with a 1 mm slice thickness and a high-resolution CT algorithm. Typically, a non-contrast chest CT was performed, with images being obtained during end-inspiration breath hold. Imaging disease extent/severity was estimated according to the COVID visual assessment scale (CoVASc), which is a visual assessment scale that roughly estimates the percentage of pulmonary parenchyma affected by COVID-19, as seen on chest CT, when both lungs are evaluated as a whole (0%, 1%-10%, 11%-25%, 26%-50%, 51%-75%, > 75%)[21].

Bias

Since this a single center study there was no bias regarding management. Since COVID-19 presents with stages of evolution[20], in order to overcome potential bias of delayed admission, we recorded and present mean time to admission when indicated

Treatment scheme

By February 2021, Greece had experienced three waves of COVID-19 pandemic, March to April, September and December 2020. Admitted patients were evaluated from the infectious disease department who decided about the therapeutic protocol based on the clinical picture and the available international therapeutic data. Five patients, who were admitted during the 1st wave, were mildly symptomatic, without severe pneumonia.

They received hydroxychloroquine plus azithromycin as per infectious department protocol[22]: A loading dose of 200 mg of hydroxychloroquine at day 1, followed by 100 mg twice per day for 5 d and azithromycin 500 mg daily for 5 d.

During the 2nd and 3rd wave the aforementioned protocol for mild disease was abandoned, as data questioned its efficacy[23]. Admitted patients requiring supplementary oxygen due to COVID-19 pneumonia to maintain SaO2 > 93%, received 6 mg intravenous dexamethasone for up to 10 d or until discharge, if sooner. Based on clinical judgment for concurrent microbial pneumonia, patients receiving dexamethasone were also prescribed azithromycin at a dose of 500 mg on day 1, and 250 mg on the four following days. An electrocardiograph to exclude long QT was performed in advance for both hydroxychloroquine and azithromycin prescription. Low molecular weight heparin was prescribed at a prophylactic dose in all admitted patients at a dose of 3500 benzaparin (body weight > 60 kg) and 2500 iu (body weight < 60 kg). On dialysis day it was given during the dialysis session. Patients who experienced an incident thromboembolic event or those who were highly suspected to have thromboembolic disease were managed with therapeutic doses of anticoagulant therapy.

Dialysis scheme

Hemodialysis was performed in an isolated room, regularly three times per week, according to the related practice guidelines as described by others[24]. Blood access status was regularly recorded, as well as events necessitating intervention (hypokalemia, hypotension, thrombosis).

Statistical methods

Patients' data was analyzed on an exploratory basis. Continuous variables were summarized with the use of descriptive statistical measures [median and interquartile range (25th, 75th percentile)], and categorical variables were displayed as frequency tables (*n*, %). Statistical tests used to check univariate associations between categorical

or continuous variables and outcomes were Pearson's chi-squared test, Fisher's exact test, *t*-test or Wilcoxon rank-sum test as appropriate. Box plots were used to visualize the laboratory data at admission and at their highest/Lowest value. The level of 5% was used for statistical significance. All statistical analyses were performed using STATA/SE 16.1 software (Copyright 1985–2019; Stata Corp LP, College Station, Texas, United States).

RESULTS

Participants

Of forty patients, who were eligible to be included in the study, thirty two were finally included, since two patients were discharged from hospital in less than 5 d, one had been diagnosed with COVID-19 for more than a week, one had active cancer, one had active autoimmune disease, one had been on hemodialysis for less than 3 mo and two had acute on chronic kidney disease, necessitating hemodialysis only temporally.

Descriptive data

The study included 32 patients on MHD, who were infected with SARS-CoV-2, were diagnosed with nasopharyngeal PCR and were hospitalized for more than 10 d until discharge or death. Five of them were diagnosed during the first wave and the rest presented during the second and third waves. As shown in Table 1, they had a median age of 75.5 (IQR 58.5-82) and 17 of them were males (53.1%). The prevalent co-morbidity was arterial hypertension found in 20 patients (62.5%), followed by diabetes mellitus in 10 (31.3%) patients. The median number of comorbidities was 3 (IQR 2-3.5). The median frailty index was 3 (IQR 2-5). Diagnosis was made by routine screening in 12 (37.5%) cases or because of symptoms suggestive of COVID-19 (62.5%). The symptoms included fever in 13 (65%), upper respiratory symptoms (dry cough, dyspnea) in 6 (30%) and diarrhea in 1 (5%). None of the patients reported anosmia, while 1 (3.125%) reported ageusia. In order to exclude potential confounders of delayed admission to the hospital

we recorded the median time to admission. It was 2 d (IQR=1-3, min = 0, max = 5) for symptomatic patients and 1 d (IQR= 0.5-1) for those diagnosed after routine screening.

According to the WHO severity score on admission, 50% of patients[16] presented with mild and 40.6% with moderate disease[13], while severe disease was observed only in 3 (9.4%) patients. No patient presented with critical disease.

Regarding radiological characteristics on admission, all except one patient, had a chest CT on admission. The patient without chest CT was asymptomatic and had a normal chest X-rays on admission. The majority of patients, *i.e.* 24 (77.4%) had CoVASc 0%-10% score, *i.e.* low grade pulmonary infiltrates, corresponding to mild and moderate WHO. Of the remaining 7 patients with CoVASc > 10%, 4 had a score of 11%-25%, corresponding to moderate disease, 2 patients with CoVASc 26%-50% and 1 patient with score 51%-75% corresponded to severe WHO disease group.

Comparison of patients who were admitted with mild *vs* those with moderate/severe disease (16 patients in each group) (Table 2), revealed that they differed only regarding the presence of symptoms. Asymptomatic patients were mostly in the mild group[11,16] *vs* 1/32 in the moderate group with statistical significance ($P = 0.001$). Age, frailty index, sex, number of comorbidities, CoVaSc CT score were not statistically different.

Treatment scheme

Sixteen patents (50%) received therapy for COVID-19, including hydroxychloroquine plus azithromycin. Thirteen patients (40.6%) received dexamethasone plus azithromycin. One patient developed severe COVID-19 pneumonia, despite dexamethasone treatment, and was further deteriorated to severe acute respiratory distress syndrome. He was treated with tocilizumab (8 mg/kg once) and he was gradually improved and was discharged with no need for oxygen support. Broad spectrum antibiotics were prescribed in case of suspected superimposed bacterial pneumonia, or other in-hospital infections in 17 (53.1 %) cases.

Characteristics related MHD

The mean time in dialysis prior to COVID-19 was 4 years. The most prevalent primary disease was arterial hypertension. Arteriovenous access was arm fistula in 15 (46.8%) patients, graft in 2 (6.2%) and ventral venous catheters in the rest. Potassium supplementation during dialysis was required in 12 patients (37.5%). Hypotensive episodes were recorded on 17 patients (53.1%). Thromboembolic events associated with access were recorded in 5 patients (15.6%).

Outcome data

"Progressors" ***vs.*** **"non-progressors":** Thirteen patients (40.6%) patients experienced progression of COVID-19, manifesting as respiratory deterioration, which occurred 7-10 d after documentation of the infection (Table 1). "Progressors" (eight males and five females) had a median age of 78 (IQR 75-82) years and a median frailty index 3 (IQR 2-5). Eight of them (66.7%) had very limited findings in the CT of the chest on admission (< 10%) and four patients had moderated findings (> 10%). Five patients (38.5%) presented with mild disease on admission, 5 (38.5%), with moderate disease, and 3 (23.1%) were asymptomatic. The median time to admission was similar between "progressors" [median 1 (IQR 1-3) day] and "non-progressors" [median 1 day (IQR 1-2) (P = 0.68)]. Ten of "progressors" were diagnosed with symptoms (76.9%) while 3 with screening.

Comparison between "progressors" *vs* "non-progressors" did not reveal any difference in terms of age, gender, frailty. Those patients who did not progress tended to have higher percentage of mild disease, but did not differ statistically form "progressors" (P = 0.095). Compared to stable patients, "progressors" tended to be older (median age 78 *vs* 70, P = 0.087), and experienced more respiratory symptoms on initial presentation (50% *vs* 10%, P = 0.14).

Survivors ***vs*** **non- survivors**: Overall (Table 1), 27 (75.8%) patients were discharged from hospital, after a median hospitalization time of 22 days (IQR = 15-35). Five patients died (Table 2) (CFR 15.6%) within a median time to death of 35 d (IQR 24-35). The

deceased *vs* survivors differed in being more frail (medians 7 *vs* 3, $P = 0.016$), with worse WHO severity ($P = 0.05$) and having a worse CT on admission ($P = 0.005$).

There were three cases of COVID-19 related death (respiratory failure), all among "progressors" (23%). Two of them died after they had been intubated and transferred to the intensive care unit. They were 2 females and 1 male, aged 75-80 years old, with frailty index on admission 2,8, and 3 respectively. All 3 died from COVID-19 related death had CoVASc > 10% on chest CT and they had moderate (2 cases) or severe (1 case) disease on admission.

Two deaths, non-related to COVID-19, were recorded in female patients, aged 70 and 85 years with recorded time to death being in 24 and 35 d respectively from admission. The frailty index was 7 in both cases and the cause of death was sudden cardiovascular event and aspiration respectively.

Laboratory analysis: Laboratory parameters on admission did not show any statistically significant association with outcome, either death or progression of COVID 19 (Table 3). There was a trend, though, for "progressors" and non-survivors to present with lower levels of lymphocytes, higher CRP and NLR (neutrophil to lymphocyte ratio) values, compared to patients who remained stable thereafter, and the survivors. "Progressors" had also a trend for higher numbers of neutrophils and level of serum ferritin values on admission. (Table 3, Figures 1 and 2).

We found a statistically significant difference between "progressors" and stable patients, regarding the highest value of 10 days of neutrophils [6800 (IQR 5300-9600) *vs* 4600 (IQR 2700-5600), $P = 0.018$] the highest value of NLR [13.4 (IQR 7.7-26.3) *vs* 3.3 (IQR 2-5.3) $P = 0.001$], and the related % increase [235.9 (IQR 18.4-394.4) *vs* 2.5 (-31.5-25.9), $P = 0.005$].

Comparison between non-survivors *vs* survivors, revealed that the former differed significantly regarding the highest value of LDH [median 313 (IQR 272-330) *vs* 225.5 (IQR 183-256), $P = 0.028$] and its % increase [89.7% (IQR 5-97.5) *vs* 5.6% (-13.8-25.2) increase, $P = 0.039$]. Additionally, non-survivors had the lowest 10^{th}-day value of

albumin [median 2.9 g/dL (IQR 2.7-3.1] *vs* [3.5 (2.9-3.7), *P* = 0.028], and the highest 10th-day value of d dimers [median 3503 ng/mL (3447-5032) *vs* 1624 (1073-2526), *P* = 0.011]. Troponin levels did not show any statistically significant difference neither in deceased patients nor in progressors.

DISCUSSION

Key results

This article analyzes our experience with COVID-19 in a cohort of 32 patients on MHD during an 11-month period before COVID-19 vaccination was available. The aim of the study was to describe the clinical characteristics of the disease at presentation, its outcomes in this group of patients, and look for distinctive features predicting outcome. According to our findings, age, gender and the presence of co-morbidities did not show any statistical difference between survivors and non- survivors and between "progressors" and "non- progressors". On the contrary, the frailty index, the WHO severity score and the CoVASc score on admission seemed to matter, since they differed statistically between survivors and non-survivors. In terms of laboratory parameters at the time of admission, a more "inflamed" laboratory profile (CRP, NLR) and lower lymphocytes were shown to be a potential alarm for adverse clinical evolution ("progressors and deceased patients"). However, the kinetics of inflammation markers (NLR, neutrophils) over ten days of hospitalization were able to distinguish with statistical significance "progressors" *vs* "non-progressors". In addition, the kinetics of LDH, d-dimers (increase) and albumin (decrease) were able to distinguish with statistical significance non-survivors from survivors.

Interpretation

The vast majority of MHD patients in our study (90. 6%) presented with mild (50%) or moderate (40.6%) severity of COVID-19, according to the WHO classification system. Apart from symptoms, being statistically more prevalent in moderate disease, the severity groups did not differ statistically regarding age, gender, number of co-

morbidities or CoVASc radiology data. In relation to this, a recent study which compared patients on chronic dialysis with a propensity matched cohort found that dialysis patients had a less severe COVID-19 phenotype[25]. In the present study, twelve patients were diagnosed by screening (37.5%) and 20 (62.5%) with symptoms, mainly fever (65%), respiratory (30%) and diarrhea (5%). Interestingly, no patient complained of anosmia or ageusia, in contrast to the general population, as reported by others as well[26]. Anosmia and ageusia have been attributed to the fact that angiotensin-converting enzyme II has been identified as the cellular receptor for SARS-CoV-2, which is found in the oral cavity and nasal mucosa[27-28], However, dialysis patients have been shown to have reduced angiotensin-converting enzyme II plasma cell activity[29].

Despite the relatively mild initial presentation, 40.6% of patients experienced progressive disease of the respiratory system. The CFR in our cohort was 15.5%. Four of the deaths occurred among "progressors" (30.7%), with three of them being related to COVID-19 (9.3%). Non-COVID-19 related death (sudden death and aspiration) was in 6.2%, one in "progressors" and one in "non-progressors". In a dialysis population of similar size from Spain[11], the CFR was reported in 30.5%. However, the Spanish cohort had worse disease status at presentation, with poor oxygen saturation (< 95%) in breathing room air observed in 22 out of 36 patients[11]. Accordingly, in a cohort study of ICU patients, the rate of death related to COVID-19, differed in dialysis patients compared to the general population, with higher prevalence of sudden death/arrhythmia and septic shock in the dialysis population[12].

Patients on chronic dialysis have been reported to be either more vulnerable[11-12] or rather protected[13-14,25]. An international study including dialysis patients concluded that these patients were both more susceptible to severe COVID-19 disease and experienced increased mortality, although with great disparity in mortality rates[30].

In clinical practice, the most challenging question is the identification of prognostic factors, which might help clinicians to recognize those patients at high risk for disease progression and/or death. We did not find any specific clinical characteristics or radiology indexes that could discriminate "progressors" from stable patients on

admission. The clinical implication, in the setting of chronic dialysis, is that even almost asymptomatic patients were candidates for disease aggravation. In the general population, the CT severity score, inflammatory markers and older age on admission have been described as independent risk factors for short-term progression[31-32].

From the laboratory perspective, on admission there was a trend in the "progressors" group, of lower lymphocytes count and higher NLR, CRP and ferritin values, *i.e.* a more inflammatory profile, as previously shown[25]. These laboratory parameters have been associated with severe COVID-19 in the general population[32-36] as well.

However, follow up of laboratory measurements revealed that there was a statistically significant increase of neutrophils and NLR during the first 10 d, between "progressors" and stable patients. Similar findings have been reported for laboratory data on 7th day after admission for dialysis patients with COVID-19[11]. Also, CRP has been used in hospitalized patients with COVID-19 for disease stratification and prognostication[36]. However, in our cohort there was only a trend for the value of day 10 for the "progressors".

In terms of survival, the WHO severity score on admission, the frailty index and the CoVAsc radiology data were shown to differ between survivors and non-survivors. Interestingly, no difference was found in clinical and radiological data on admission between "progressors" and "non-progressors". Yet, death occurred also from non COVID-19 respiratory failure, *i.e.* non-COVID19 related. Zeng *et al*[37] compared the annual all-cause mortality in dialysis patients during the pandemic and found that it was significantly higher in 2020 (4.89%) than in 2018 (2.55%) or 2019 (1.97%). During the COVID-19 outbreak, the mortality rate from all causes excluding COVID-19 was 2.73%, which was slightly higher than that from COVID-19 (2.16%). In our cohort, we recorded a rate of 5.9% non-COVID-19 related deaths. As has been reported[2], patients with severe underlying diseases often die with COVID-19, *i.e.* they die of their original co-morbidities. In our cohort, as in the large ERA-CODA[6] the frailty index in contrast to co-morbidities, discriminated survivors from non-survivors patients in chronic dialysis.

None of the laboratory parameter on admission could discriminate survivors from non-survivors, except a tendency for lower lymphocytes, and higher CRP, NLR and d-dimers values on admission, *i.e.* a more inflammatory profile. Importantly, follow up of the laboratory values over 10 d revealed that non-survivors differed significantly from survivors only regarding the 10th-day value of LDH, d-dimers (higher values) and the lowest 10th-day value of albumin. The sequential increase of LDH has been described as a prognostic laboratory marker for severe COVID-19 in the general population[38] and dialysis patients[11,39], indicating cytokine-induced lung tissue damage[38]. Increased levels of d-dimers have also associated with adverse outcomes in COVID-19 patients both in the general population[40] and in patients on MHD[39]. Interestingly, troponin levels did not show any significant difference neither in deceased patients nor in "progressors". Troponin levels have been described as a predictive marker of COVID-19 mortality in the general population[33], a finding which was not confirmed in dialysis patients[39]. This is probably related to the fact that troponin levels in patients with chronic kidney disease may be related to chronic structural heart disease rather than acute ischemia[41].

Due to the small number of patients we cannot draw any conclusions on the effect of treatment. During the 1st wave the combination of hydroxychloroquine and azithromycin was given only in 3 symptomatic patients, all of whom survived. However, they had all presented with very mild disease, low CoVASc score (< 10%) although they were quite old and moderately frail. This type of treatment has not been shown efficient for mild and moderate COVID-19[42]. During the 2nd wave, there was no specific treatment, except the use of dexamethasone, in patients who required administration of oxygen, according the recovery trial[43]. Azithromycin was given based on its antiviral and immunomodulatory activity[44]. No adverse effects were recorded[45]. A patient who did not respond to dexamethasone during the 3rd wave received tocilizumab for severe pneumonia and showed remarkable improvement[46].

In general, ESKD is associated with increased mortality rates compared to age-matched controls[47], especially death from cardiovascular events[48] and in the intensive

care unit[49]. Since cardiovascular complications are rapidly emerging as a key threat in COVID-19 in addition to respiratory disease[50], it would be expected that this "fragile" population would be devastated by the pandemic. Patients with ESKD were shown to have the paradox of immune-activation and immune-depression[51] at the same time. For the general population a unique immune response to SARS-CoV-2 has been described[52]. It has been proposed that ESKD patients may be rather protected for severe COVID-19, as unable to mount a cytokine hyper-active response, a cardinal feature of severe COVID-19[14]. Thus, being in chronic dialysis may not always an independent risk factor for COVID-19 adverse outcome[39].

CONCLUSION

In conclusion, here in we describe a cohort of patients in chronic dialysis who were admitted with COVID-19. A proportion of patients were diagnosed following routine testing and presented with mild disease. Absence of pneumonia or mild pneumonia was documented clinically on admission in 90.6% of patients, while CT tomography revealed infiltrates > 10% only in 13.3% of admitted patients. A CFR of 15.6%[5,32] was recorded in the whole cohort and 30.7% among "progressors". On admission a more "inflamed" profile reflected in CRP, WBC, NLR and lower lymphocytes indicated a "hint" for upcoming progress to respiratory failure, although with no statistical significance. Clinically, a statistical significance for disease progression was shown by the highest 10th-day value of NLR, and its % increase from admission, and the highest 10th- day value of neutrophils. As for survival, the frailty index, the severity stage by WHO classification and the CoVASc score were shown statistically different the ones on admission. Likewise, the highest 10th -day value of LDH and d-dimers and the lowest of albumin were shown important. Further studies are needed to unravel the immune response to COVID-19 in chronic dialysis patients and stratify the best management algorithm.

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