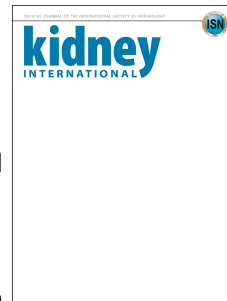




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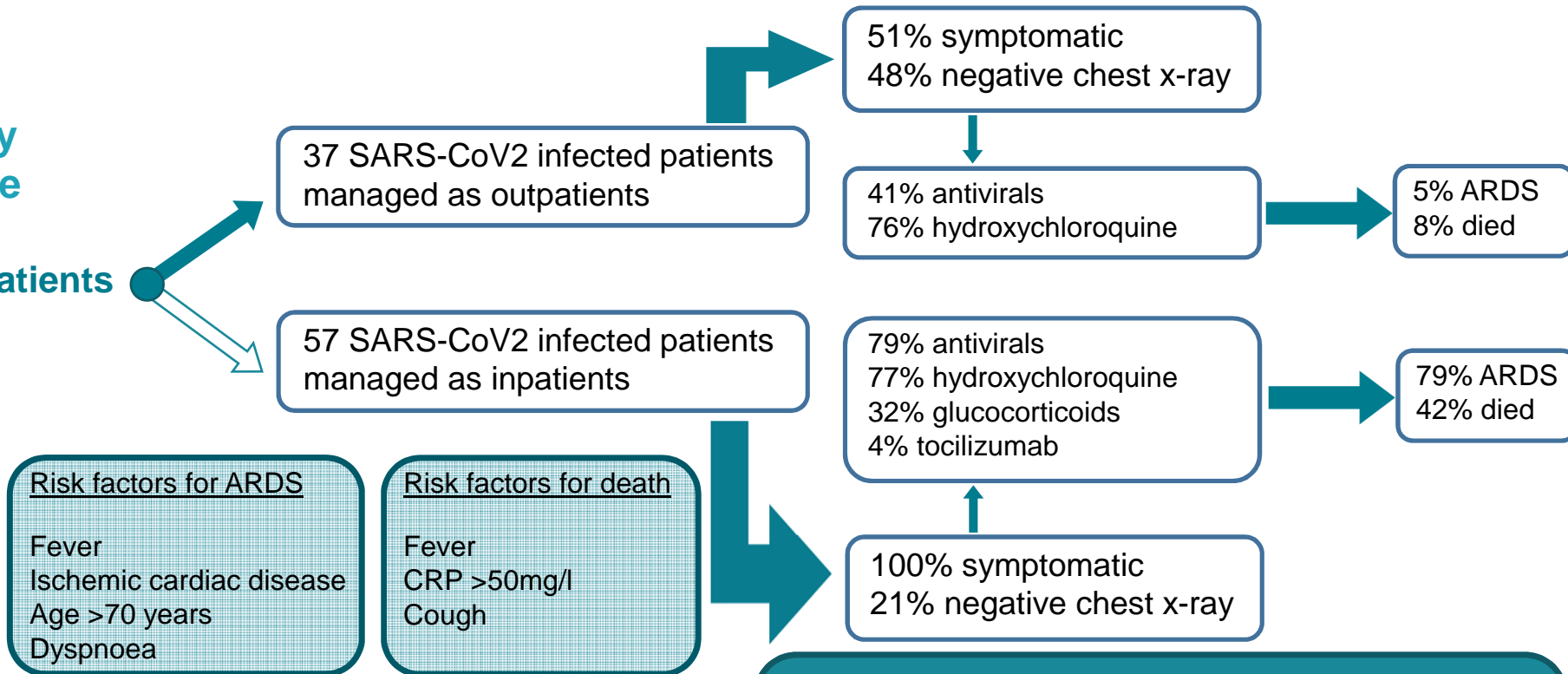
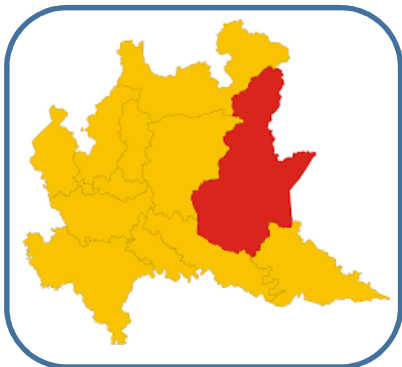
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A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection.

Lombardy – Italy
Brescia province

643 hemodialysis patients



CONCLUSION:

Variable disease severity for SARS-CoV2 infection in haemodialysis patients. High risk for ARDS and death in the subgroup requiring hospital admission

A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection.

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Abstract

The SARS-CoV-2 epidemic is pressuring health care systems worldwide. Disease outcomes in certain subgroups of patients are still scarce, and data are needed. Therefore, we describe here the experience of four dialysis centers of the Brescia Renal COVID task force. During March 2020, within an overall population of 643 hemodialysis patients, SARS-CoV-2 RNA positivity was detected in 94 (15%). At disease diagnosis, 37 of the 94 (39%) patients (group 1) were managed on an outpatient basis whereas the remaining 57 (61%) (group 2) required hospitalization. Choices regarding management strategy were made based on disease severity. In group 1, 41% received antivirals and 76% hydroxychloroquine. Eight percent died and 5% developed acute respiratory distress syndrome (ARDS). In group 2, 79% received antivirals and 77% hydroxychloroquine. Forty two percent died and 79% developed ARDS. Overall mortality rate for the entire cohort was 29%. History of ischemic cardiac disease, fever, older age (over age 70) and dyspnea at presentation were associated with the risk of developing ARDS whereas fever, cough and a C-reactive protein higher than 50 mg/l at disease presentation were associated with the risk of death. Thus, in our population of hemodialysis patients with SARS-CoV-2 infection, we documented a wide range of disease severity. The risk of ARDS and death is significant for patients requiring hospital admission at disease diagnosis.

Introduction.

The impact of the SARS-CoV-2 epidemic in subgroups of patients has yet to be determined. In Brescia, Italy we have developed a standardized protocol when approaching patients on maintenance haemodialysis (MHD) and kidney transplant recipients, respectively (1). Reports would suggest a more severe disease course in patients with CKD(2) although outcomes in MHD patients is still unclear with earlier small case series suggesting a milder course (3). Management of MHD patients in the context of an epidemic poses several challenges: this group of patients usually requires caregiver assistance, transportation from home to the dialysis units as well as spending periods of time in crowded waiting areas before and after treatment(4). Moreover, MHD patients are usually old and affected by several comorbidities that are known to be associated with high risk of poor outcomes in patients with COVID-19. The Lombardy region in general and Brescia in particular have been severely hit by the SARS-CoV-2 epidemic and this has generated several logistical and clinical challenges for the dialysis units of the “Brescia Renal COVID task force”. Here, we describe the characteristics and outcomes of the MHD patients affected by COVID-19 and followed in four dialysis units that are a part of the “Brescia Renal COVID task force”.

Results

Ninety-four patients tested positive for RT-PCR within the overall population of 643 (15%) (**Table 1**). While 3 centers limited the viral testing only to patients showing symptoms suggestive for SARS-CoV-2 infection, the center of Brescia performed RT-PCR in its entire MHD population (patients with symptoms and patients without symptoms). The positivity rates were not substantially different between these approaches (14% versus 16%, respectively). Patients testing positive were either triaged to the hospital or back to their

dialysis facility based on the clinical judgement of the caring physician according mainly to the severity of the symptoms shown. The main clinical characteristics of the overall MHD population with SARS-CoV2 infection and the subgroups managed as outpatient or in hospital are shown in **Table 2**. The median time from symptoms onset to positive RT-PCR was 2 days (IQR 0-3). Patients that needed to be admitted showed a higher proportion of symptoms compared to the ones not requiring hospitalisation (46% vs 14%).

Outpatient management

Thirty-seven out of 94 (39%) patients were managed as outpatients, for a median follow-up of 8 days (IQR 6-11). Among the group managed as outpatient, 18/37 (49%) were asymptomatic at disease diagnosis, while the remaining patients experienced mild symptoms. Among the asymptomatic patients, in 13/18 (72%) the chest x-ray was negative, while unilateral and bilateral infiltrates were detected respectively in 3/18 (17%) and 2/18 (11%). Detailed patient characteristics are shown in **Table 2**.

Antiviral therapy and/or hydroxychloroquine were employed in 28/37 (76%) patients for a median duration of 4 days (IQR 3-8). Antibiotics were employed in 25/37 (68%): macrolides in 56%, cephalosporins in 48%, carbapenems in 8%, glycopeptides in 8%, aminoglycosides in 8%, beta-lactams in 4% and fluoroquinolones in 4%. 4/37 (11%) received prophylactic heparin and 3/37 (8%) were on ACEi or ARBs.

One patient had to withdraw hydroxychloroquine due to vomiting. No other adverse event due to the treatment was documented in this patient group.

During follow-up, 7/37 (19%) patients experienced a new onset/a worsening of the interstitial pneumonia, 3/37 (8%) died, 2/37 (5%) developed ARDS and 2/37 (5%) had to be hospitalized. In addition, 5/37 patients (14%) developed cough, 5/37 (14%) myalgia, 4/37 (11%) fever and 3/37 (8%) gastrointestinal symptoms during follow up.

Patients who were asymptomatic at baseline, compared to the symptomatic ones, were less likely to develop ARDS (0/18 vs 2/19), to develop a new onset or a worsening of pneumonia (1/18 vs 6/19) and less likely to die (0/18 vs 3/19).

Hospitalized patients

Fifty-seven patients were admitted after a median time from symptom onset and from positive RT-PCR test results of 4 (IQR 1-7) and 2 days (IQR 1-3), respectively. Median follow-up was 8 days (IQR 4.8-15). Detailed characteristics of this population are shown in **Table 2**. Antiviral therapy was employed in 45/57 (79%) with 13/45 patients (29%) experiencing adverse events: 7 diarrhoea, 4 increase in liver enzymes, 3 prolongation of QTc interval, 2 atrial fibrillation, 1 gastrointestinal bleeding, 1 coagulation alterations and 1 skin rash. The median duration of lopinavir/ritonavir or darunavir + ritonavir and hydroxychloroquine treatments were 7 days (IQR 5-12) and 5 days (IQR 3-7), respectively. Antibiotics were administered in 55/57 patients: macrolides in 40%, cephalosporins in 49%, carbapenems in 15%, glycopeptides in 20%, aminoglycosides in 7%, beta-lactams in 25% and fluoroquinolones in 24%. Thirty one out of 57 (54%) received prophylactic heparin and 11 out of 57 (19%) were on ACEi or ARBs.

Forty-five out of 57 patients (79%) developed ARDS; 24/57 (42%) died after a median of 6 days (IQR 3.8-9.5) from admission and a median of 9 days (IQR 7-10) from onset of symptoms. Eleven out of 57 (19%) patients were discharged after a median of 8 days (IQR 6.5-13) from admission and 15 days (IQR 12.5-17.5) from onset of symptoms. Among the patients who died, the cause of death was respiratory failure secondary to ARDS in 15/24 (63%), bacterial sepsis in 4/9 and sudden death of unknown origin in 5/9.

Serial chest x-rays were performed in 27/57 (47%) patients; among those patients 20/27 (74%) showed chest x-ray worsening compared to baseline.

Dexamethasone was administered to 18/57 (32%) patients due to respiratory deterioration; 2 out of 18 of these patients also received tocilizumab. In this group, 5 out of 18 patients (28%) died. Out of 9 patients whose response to glucocorticoids was assessable at the moment of data analyses, 2/9 showed stabilisation of the pO₂/PIF ratio or chest x-ray improvement, while the remaining patients did not improve. Regarding the two tocilizumab treated patients, response was assessable only in one with no improvements in chest x-ray or lung function.

Factors associated with risk of ARDS and death

In univariate analyses, cardiac failure (OR 6.22 (95%CI 1.85-28.6), p=0.007), ischemic heart disease (OR 5.61 (95%CI 1.65-25.9), p=0.01), fever at disease diagnosis (18.2 (95%CI 5.6-82.44), p=0.000013), shortness of breath at disease diagnosis (18.17 (95%CI 4.8-119.5), p=0.0002), myalgia or fatigue at disease diagnosis (OR 5.6 (95%CI 1.65-25.9), p=0.01), infiltrates at the baseline chest X-ray (OR 4.4 (95%CI 1.67-13), p=0.004), higher AST levels (OR 2.81 (95% 1.08-7.6), p=0.04) and higher CRP levels (OR 4.68 (95%CI 1.83-12.7), p=0.002) were associated with the risk of developing ARDS. Ischemic heart disease (OR 3.11 (95%CI 1.02-9.6), p=0.05), fever at disease diagnosis (OR 18.7 (95%CI 3.62-343), p=0.005), cough at disease diagnosis (OR 3.5 (95%CI 1.28-9.7), p=0.01), shortness of breath at disease diagnosis (OR 5.3 (95%CI 2-15), p=0.001) and higher CRP at disease diagnosis (OR 6 (95%CI 2.1-19), p=0.001) were associated with the risk of death (**Table 3**).

Two multivariate analyses were performed, one for each outcome of interest (ARDS and death). In the first model, the characteristics found to be associated with the risk of ARDS were history of ischemic heart disease (OR 7.5 (95%CI 1.6-36.2), p=0.04), fever at disease diagnosis (OR 17 (95%CI 4.5-64), p=0.0009), age at symptoms onset (OR 1.1 (95%CI 1-1.15), p=0.03) and shortness of breath at disease onset (OR 20, (95%CI 3.6-79.3), p=0.004). In the

second model, the characteristics associated with the risk of death were fever at disease diagnosis (OR 18.7 (95%CI 2.4-146), $p=0.02$), cough at disease diagnosis (OR 4 (95%CI 1.02-17.6), $p=0.05$) and higher serum CRP at disease diagnosis (OR 5.6 (95%CI 1.6-23.5), $p=0.01$) (**Table 4**).

Discussion

SARS-CoV-2 infection is challenging health care systems around the world. The predictions regarding Covid-19 associated mortality are changing as new information is gathered although comorbidities such as cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and cancer are consistently associated with worse prognosis(5, 6). We have reported recently that hospitalized kidney transplant recipients tended to have a poor prognosis with a mortality rate of 25%(7), while another group observed that when such patients did not require hospital admission they experienced a more favourable outcome(8).

The prognosis of haemodialysis patients with COVID-19 is still unclear and more data are desperately needed. In our cohort including four centers of the “Brescia Renal COVID task force”, we have identified 94 patients with SARS-CoV-2 infection. As expected, infected MHD patients not requiring hospital admission experienced a better disease course compared to patients who required hospitalisation. Nevertheless, 5% of the patients treated in the outpatient setting subsequently required admission. There was also substantially less use of antiviral medications in patients managed in the outpatient setting although the proportion of patients receiving hydroxychloroquine was similar between the two groups. This should be taken into account when interpreting the results since it was the managing physicians decision to start medications. While the lower rate of antiviral use was associated with lower incidence of adverse events in the outpatient group, whether this may be the result of less frequent antiviral use rather than a better overall disease profile needs to be clarified. Finally, in our cohort, only a few patients were treated with glucocorticoids and tocilizumab, which does not allow us to draw any conclusions on the potential efficacy of these treatments.

The disease severity of the SARS-CoV-2 infection is highly variable and a significant proportion of infected patients appear to experience only mild disease or no symptoms at all in our cohort. Notably, the overall case fatality rate of our population was higher compared to

the general Italian and Chinese population (28% vs 7.2% vs 2.3%)(9, 10). The finding of worse outcome of hemodialysis patients with SARS-CoV-2 infection may be explained by high prevalence of comorbidities as well as other risk factors related to end stage renal disease *per se* (2).

Our study also provides some preliminary information on factors associated with the risk of ARDS and death. The presence of CVD and severe inflammation were predictive of worse outcomes. Notably, these factors are not specific for the haemodialysis population since cardiac comorbidities, fever and older age have been already described as prognostic factors in the general population with SARS-CoV-2 infection(11, 12).

Our results should be interpreted with some caution. Median follow-up was 8 days, center bias cannot be ruled out, symptoms severity was not collected, and the relatively small sample size of our cohort may have impacted on the generalizability of our analyses. The strengths of our study include a shared management approach characterized by relative data homogeneity and detailed data collection made possible by an unprecedented commitment of the members of our task force.

In conclusion, SARS-CoV-2 infection in maintenance haemodialysis patients presents with a wide range of symptoms. The data represented herein suggest a strikingly higher mortality rate compared to the general population although the risk factors for disease severity are similar. Further data collection and follow up is necessary to have a complete picture of the spectrum of COVID-19 in maintenance dialysis patients.

Methods

From March the 1st to April the 3rd 2020, we enrolled all haemodialysis patients with SARS-CoV-2 infection who were managed within four haemodialysis hubs (**table 1**) of the “Brescia Renal COVID task force”. Each one of these dialysis centers implemented general prevention

measures to safeguard their population. Three of the four haemodialysis hubs reserved the RT-PCR test only to patients showing symptoms suggestive of the disease, after their referral to dedicated clinics. Conversely, starting on March the 20th, the Brescia dialysis unit performed the RT-PCR on all patients followed.

The therapeutic strategy followed our protocol(1). Antiviral therapy based on Lopinavir/Ritonavir associated to hydroxychloroquine (with dose adjusted according to kidney function) was considered for all patients, if not contraindicated. In case of shortage of Lopinavir/Ritonavir, Darunavir and Ritonavir were employed. Patients experiencing clinical deterioration after at least 7 days following symptom onset, or no fever for >72h, with escalating oxygen requirements, progression of the chest x-ray and no signs of bacterial infection, were considered for dexamethasone (20 mg/daily for 5 days, then 10 mg/daily for 5 days) and up to two tocilizumab infusions at an interval of 12-24 hours (8 mg/kg of body weight, maximum dose per infusion 800 mg).

Considering the well-known potential of lopinavir/ritonavir and hydroxychloroquine for increasing QTc, a baseline EKG was performed before therapy commencement and, afterwards, every 2-3 days; in case of QTc prolongation a reduction or discontinuation of treatment was considered in a case-by-case manner.

Acute respiratory distress syndrome (ARDS) and cardiac failure have been defined as reported by others (13, 14). The decision whether or not admitting a patient was taken by the attending physician according to symptoms severity or signs of respiratory failure.

Ethical approval for this study was obtained according to Italian regulations.

Statistical analyses

Statistical analysis was performed using R software (<https://www.r-project.org>) and GraphPad Prism 7. Results are expressed as the number and percentage for categorical variables and the median (interquartile range [IQR]) for continuous variables.

Changes in variables were compared by a related sample Wilcoxon test, proportions of patients were compared using a chi-squared or Fisher test, as appropriate.

Univariate and multiple logistic regression models were used to assess the ability of some predefined clinical characteristics to predict the risk of ARDS or death. All the statistically significant predictors at univariate analysis were entered in a multivariate model (15). Finally, the best multivariate model was identified by adopting a stepwise selection approach. Odds ratios (ORs) and their 95% CIs were estimated from logistic regression analysis. P values less than 0.05 (2-tailed) were considered significant.

TABLES

Table 1. Haemodialysis patients with SARS-CoV2 infection in four dialysis centers of the “Brescia Renal Covid Task Force”.

Center	Positive Admitted	Positive Outpatients	Positive Overall	Overall population	Percentage of positive patients
Brescia	25	22	49	302	16%
Chiari	16	14	30	155	19%
Manerbio	12	0	12	99	12%
Montichiari	4	1	5	87	6%
TOTAL	57	37	94	643	15%

Table 2. Baseline clinical characteristics of 94 haemodialysis patients affected by SARS-CoV-2 infection and followed within four centers of the “Brescia Renal COVID task force”.

Characteristics		All patients (94)	Outpatients (37)	Admitted (57)	p value*
Male/Female		62/32	24/13	39/18	0.82
Age (years)		72 (IQR 62-79)	67 (IQR 60-77)	73 (IQR 64-80)	0.17
Cause of ESRD	Not determined	40/94 (43%)	8/37 (22%)	32/57 (56%)	0.001
	Glomerulonephritis	19/94 (19%)	15/37 (41%)	4/57 (7%)	0.0001
	Genetic diseases	15/94 (16%)	6/37 (16%)	9/57 (16%)	1
	Diabetes	11/94 (12%)	3/37 (8%)	8/57 (14%)	0.52
	Other	9/94 (10%)	5/37 (14%)	4/57 (7%)	0.31
Comorbidities	Hypertension	93%	35/37 (95%)	52/57 (91%)	0.7
	Diabetes	43%	13/37 (35%)	27/57 (47%)	0.29
	Vascular disease	23%	7/37 (19%)	15/57 (26%)	0.46
	Cardiac failure	18%	1/37 (3%)	16/57 (28%)	0.002
	Ischaemic cardiac disease	17%	4/37 (11%)	12/57 (21%)	0.27
	Cancer	12%	5/37 (14%)	6/57 (11%)	0.75
	COPD	11%	6/37 (16%)	4/57 (7%)	0.18
	Other	17%	4/37 (11%)	13/57 (23%)	0.18
Haemodialysis vintage (years)		3 (IQR 1-6)	2 (IQR 1-7)	3.9 (IQR 1.6-6.4)	0.19
Haemodialysis frequency	Twice a week	12/94 (13%)	3/37 (8%)	9/57 (16%)	0.35
	Three times a week	82/94 (87%)	34/37 (92%)	48/57 (84%)	0.35
Haemodialysis modality	HD	69/94 (73%)	26/37 (70%)	43/57 (75%)	0.64
	HDF	23/94 (25%)	11/37 (30%)	12/57 (21%)	0.46
	AFB	2/94 (2%)	0	2/57 (4%)	0.52
SARS-CoV-2 infection	Temperature (>37.5 °C)	68%	16/37 (43%)	49/57 (86%)	<0.0001

symptoms at disease onset					
	Cough	23%	6/37 (16%)	16/57 (28%)	0.22
	Gastrointestinal symptoms	6%	1/37 (3%)	5/57 (9%)	0.4
	Pharyngitis	2%	1/37 (3%)	1/57 (2%)	1
	Shortness of breath	25%	1/37 (3%)	22/57 (39%)	<0.0001
	Myalgia	17%	2/37 (5%)	14/57 (25%)	0.02
Baseline chest X ray	No infiltrates	30%	15/31 (48%)	11/53 (21%)	0.01
	Unilateral infiltrates	25%	7/31 (23%)	13/53 (25%)	1
	Bilateral infiltrates	45%	9/31 (29%)	29/53 (55%)	0.03
Baseline blood tests	WBC (NV 4,00 - 10,80 x10 ³ /uL)	5075 (IQR 3943-6470)	5960 (IQR 4095-6865)	4760 (IQR 3910-5645)	0.08
	Neutrophils (NV 1,50 - 8,00 x10 ³ /uL)	3505 (IQR 2688-4770)	4400 (IQR 2760-5330)	3430 (IQR 2680-4080)	0.1
	Lymphocytes (NV 0,90 - 4,00 x10 ³ /uL)	745 (IQR 550-1085)	900 (IQR 600-1200)	623 (IQR 510-1000)	0.05
	Platelets (NV 130 - 400 x10 ³ /uL)	162000 (IQR 126000-229500)	202000 (IQR 124250-263750)	151000 (IQR 127000-181000)	0.02
	LDH (NV 135 - 225 U/L)	254 (IQR 193-354)	218 (IQR 187-303)	352 (IQR 219-404)	0.004
	CPK (NV 39 - 308 U/L)	64 (IQR 38-138)	51.5 (IQR 33-143)	96 (IQR 49-138)	0.33
	AST (NV 18 - 54 U/L)	23 (IQR 17-35)	19 (IQR 12-24)	27 (IQR 19-46)	0.0002
	ALT (NV 10 - 50 U/L)	17 (IQR 11-25)	14.5 (IQR 10-21)	19 (IQR 13-29)	0.04
	Bilirubin (NV < 1,20 mg/dl)	0.3 (IQR 0.28-0.4)	0.28 (IQR 0.21-0.37)	0.3 (IQR 0.3-0.5)	0.05
	CRP (NV < 5,0 mg/L)	42.9 (IQR 10-82)	12.8 (IQR 3.7-33.8)	60 (IQR 19-89)	0.0004
Time from symptom onset to antiviral therapy initiation		4 (IQR 1-6)	5 (IQR 3-5)	3 (IQR 1-6.5)	0.05

Time from RT-PCR positivity to antiviral therapy initiation		2 (IQR 0-4)	3 (IQR 2-5)	1 (IQR 0-3)	0.0003
Antiviral therapy	Lopinavir/ritonavir	19/94 (20%)	0/37 (0%)	19/57 (33%)	
	Darunavir + ritonavir	41/94(44%)	15/37 (41%)	26/57 (46%)	
	Hydroxychloroquine	72/94 (77%)	28/37 (76%)	44/57 (77%)	

Data are reported as n(%) for categorical variables and median (interquartile range) for continuous variables.

Abbreviation: HD, haemodialysis, HDF, haemodiafiltration, AFB acetate free biofiltration

* Comparison between the two groups "Outpatients" and "Admitted"

Table 3. Univariate analyses of the association between clinical characteristics and the risk of ARDS or death in haemodialysis patients with SARS-CoV2 infection

Variable	Outcome ARDS		Outcome Death	
	OR (95%CI)	p value	OR (95%CI)	p value
Sex	0.68 (0.29-1.61)	0.39	1.05 (0.41-2.78)	0.93
History of hypertension	0.37 (0.05-1.83)	0.25	0.27 (0.05-1.31)	0.1
History of cardiac failure	6.22 (1.85-28.6)	0.007	1.04 (0.3-3.2)	0.94
History of diabetes	1.7 (0.75-3.9)	0.21	1.7 (0.69-4.2)	0.25
History of peripheral vascular disease	1.27 (0.49-3.36)	0.63	0.91 (0.29-2.56)	0.86
History of ischaemic cardiac disease	5.61 (1.65-25.9)	0.01	3.11 (1.02-9.6)	0.05
History of COPD	1 (0.26-3.84)	1	1.07 (0.22-4.2)	0.92
History of cancer	1.88 (0.53-7.64)	0.34	1.5 (0.36-5.4)	0.55
Type dialysis (HDF vs HD)	0.43 (0.16-1.14)	0.097	1.12 (0.38-3.05)	0.83
Age (>70 vs ≤70)	2.18 (0.96-5)	0.065	1.85 (0.75-4.78)	0.18
Fever at disease diagnosis	18.2 (5.6-82.4)	0.000013	18.7 (3.62-123)	0.005
Cough at disease diagnosis	1.61 (0.62-4.37)	0.33	3.5 (1.28-9.7)	0.01
Shortness of breath at disease diagnosis	18.17 (4.8-119.5)	0.0002	5.3 (2-15)	0.001
Myalgia or fatigue at disease diagnosis	5.6 (1.65-25.9)	0.01	2.26 (0.72-6.9)	0.15
Infiltrates at chest X ray at disease diagnosis	4.4 (1.67-13)	0.004	2.9 (0.95-11)	0.08
WBC (≤5 vs >5 x10 ³ /uL)	1.2 (0.52-1.8)	0.66	1.82 (0.73-4.6)	0.2
Lymphocytes (≤0.75 vs >0.75 x10 ³ /uL)	1.76 (0.75-4.2)	0.19	1.5 (0.59-3.9)	0.4
Platelets (≤150 vs >150 x10 ³ /uL)	1.43 (0.62-3.37)	0.41	1.9 (0.75-4.8)	0.17
LDH (>250 vs ≤250 U/l)	0.99 (0.32-3.11)	0.99	0.71 (0.18-2.7)	0.62
AST (>25 U/l vs ≤25 U/l)	2.81 (1.08-7.6)	0.04	1.85 (0.66-5.3)	0.24
ALT (>20 vs ≤20 U/l)	1.73 (0.67-4.69)	0.25	2.5 (0.88-7)	0.085
CRP (>50 mg/l vs ≤50 mg/l)	4.68 (1.83-12.7)	0.002	6 (2.1-19)	0.001
Antiviral therapy	1.29 (0.48-3.55)	0.62	0.39 (0.14-1.11)	0.08
Time from symptoms to antiviral commencement (≤5 vs >5)	2.09 (0.65-7.51)	0.23	0.55 (0.11-2.1)	0.41
Hydroxychloroquine	1.16 (0.44-3.12)	0.76	0.44 (0.16-1.24)	0.12

Table 4. Two models of multivariate analyses of the association between clinical characteristics and the risk of ARDS or death in haemodialysis patients with SARS-CoV2 infection**Model 1**

Variable	Outcome ARDS	
	OR (95%CI)	p value
History of ischaemic cardiac disease	7.5 (1.6-36.3)	0.04
Fever at disease onset	17 (4.5-64)	0.0009
Age at symptoms (>70 vs ≤70)	1.1 (1-1.15)	0.03
Shortness of breath	20 (3.6-79.3)	0.004
Myalgia or fatigue	8.5 (0.83-40.3)	0.11

Model2

Variable	Outcome Death	
	OR (95%CI)	p value
History of ischaemic cardiac disease	5 (0.94-32.3)	0.07
Fever at disease onset	18.7 (2.4-146)	0.02
Cough at disease onset	4 (1.02-17.6)	0.05
CRP at baseline (>50 mg/l vs ≤50 mg/l)	5.6 (1.6-23.5)	0.01

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