ORIGINAL ARTICLE

Identifying prognostic risk factors for poor outcome following COVID-19 disease among in-centre haemodialysis patients: role of inflammation and frailty

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Abstract

Introduction The pandemic of coronavirus disease (COVID-19) has highly affected patients with comorbidities and frailty who cannot self-isolate, such as individuals undergoing haemodialysis. The aim of the study was to identify risk factors for mortality and hospitalisation, which may be useful in future disease spikes.

Methods We collected data retrospectively from the electronic medical records of all patients receiving a diagnosis of COVID-19 between 11th March and 10th May 2020 undergoing maintenance haemodialysis at four satellite dialysis units from the Royal Free London NHS Foundation Trust, London, UK. Mortality was the primary outcome, and the need for hospitalization was the secondary one.

Results Out of 746 patients undergoing regular haemodialysis, 148 symptomatic patients tested positive for SARS-CoV-2 by RT-PCR and were included in the analysis. The overall mortality rate was 24.3%. By univariate analysis, older age, ischaemic heart disease, lower systolic blood pressure, lower body mass index (BMI) and higher frailty scores were associated with higher rates of mortality (all p value < 0.05). The laboratory factors associated with mortality were higher values of WBC, neutrophil counts, neutrophil to lymphocyte ratios (NLR), C-reactive protein (CRP), bilirubin, ferritin, troponin, and lower serum albumin level (all p value < 0.05). In the logistic regression, mortality was associated with older age and higher CRP, while high levels of NLR and CRP were associated with the need for hospitalization.

Discussion Haemodialysis patients are susceptible to COVID-19 and have a high mortality rate. Our study identifies prognostic risk factors associated with poor outcome including age, frailty and markers of inflammation, which may support more informed clinical decision-making.

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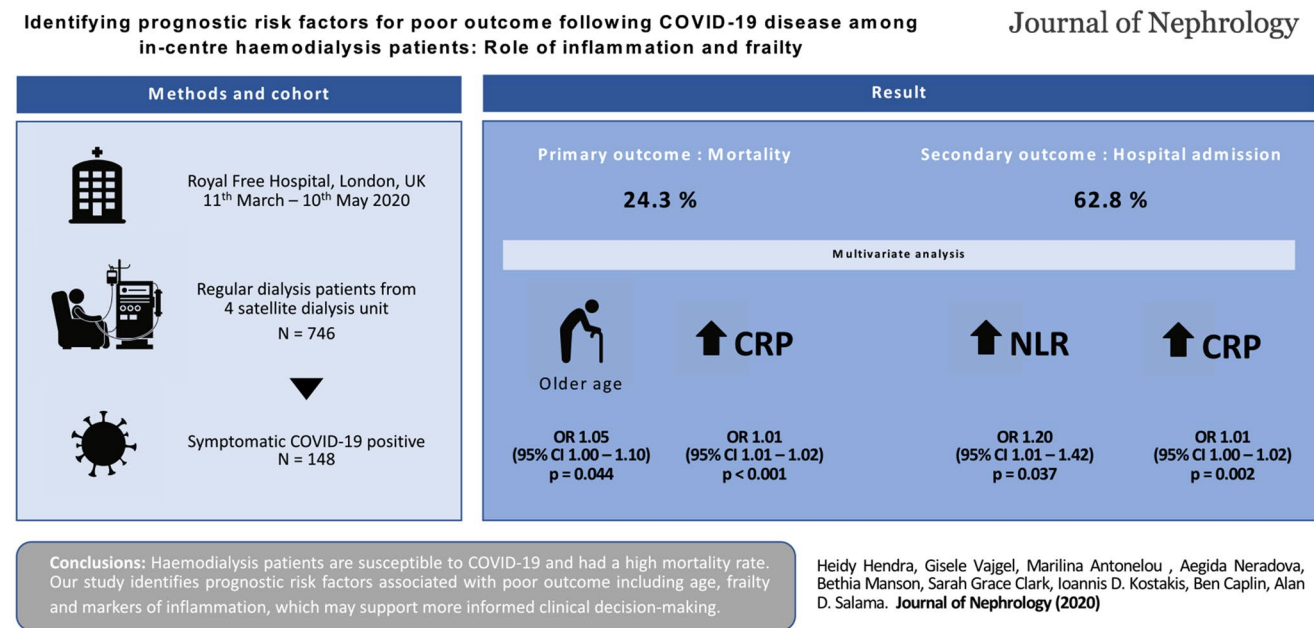   Rowland Hill Street, London NW3 2PF, UK

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Graphic abstract

Identifying prognostic risk factors for poor outcome following COVID-19 disease among in-centre haemodialysis patients: Role of inflammation and frailty

Conclusions: Haemodialysis patients are susceptible to COVID-19 and had a high mortality rate. Our study identifies prognostic risk factors associated with poor outcome including age, frailty and markers of inflammation, which may support more informed clinical decision-making.

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Abbreviations

CRP	C-reactive protein
HD	Haemodialysis
NLR	Neutrophil–Lymphocyte Ratio
RT-PCR	Real-time polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2

Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2, also referred to as HCoV-19) emerged in Wuhan, Hubei province, China [1, 2]. The World Health Organization (WHO) declared a global pandemic of the SARS-CoV-2 associated disease, COVID-19, on 11th March, 2020 due to its rapid dissemination, and as of 26th August, 2020, there are more than 23 million confirmed cases with over 800,000 deaths. In the UK, the first confirmed COVID-19 case was reported on 31st January, 2020 and since then, there have been over 320,000 confirmed cases and more than 41,000 deaths resulting in a case fatality rate of 12.6% [3].

Patients aged 70 years or older, and those with chronic comorbidities including chronic kidney disease, have been deemed highly vulnerable and at the time were advised to shield to minimize exposure [4]. However, shielding was not possible for patients with end stage renal failure (ESRF) requiring life-supporting, in-centre haemodialysis (HD) two to three times a week. Thus, a predominantly elderly, co-morbid, majority Black, Asian and minority ethnic (BAME) population, with significant comorbidities such as diabetes and cardiovascular disease, was exposed repeatedly to other patients, as well as to hospital and transport staff, multiple times a week. A single centre cohort study from West London has shown that 19.6% of the patients receiving HD tested positive for SARS-CoV-2, which placed significant pressure on dialysis staffing and resources and also highlighted the need for isolation measures [5].

Although there are some published haemodialysis cohorts reporting higher mortality rates in the United States (28–31%) [6, 7] and in Europe (25–29%) [8, 9], granular data about risk factors for mortality in this particular population remain limited.

To minimise the risk of transmission, we isolated SARS-CoV-2 positive dialysis patients and suspected cases by placing them in individual cubicles or side rooms during dialysis. No mixing took place in the dialysis centre. In addition, we avoided moving dialysis machines from areas with -SARS-CoV-2 positive patients to 'clean' dialysis areas with COVID negative patients, and we also created an isolated waiting area. There were no cohorted shifts or creation of separate 'COVID' dialysis units; the isolation occurred within the same shifts. With regard to transport, all

SARS-CoV-2 positive cases were cohorted in 'COVID positive' transport, or family members were asked to help deliver the patients, or in rare cases where none of this was possible the patients were admitted to the hospital. Suspected cases were transported alone where possible but at surge peak, cohorting of suspected cases with known SARS-CoV-2 positive patients was permissible.

The aim of the study was to describe our cohort of dialysis patients who developed COVID-19 and identify the risk factors for mortality (primary outcome) and hospital admission (secondary outcome).

Methods

Study population

This study was approved by NHS ethics committee 20/SW/0077.

Chronic in-centre haemodialysis at The Royal Free Hospital NHS Foundation Trust is carried out at four satellite dialysis units spread across North London (Barnet Dialysis Unit, Edgware Kidney Care Centre, St Pancras Kidney and Diabetes Centre and Tottenham Hale Kidney and Diabetes Centre). During the pandemic, symptomatic patients were tested at their dialysis unit or sent to the emergency department at the Royal Free Hospital to have a nasopharyngeal swab for SARS-CoV-2, clinical assessment and laboratory evaluation. As of 15th April, 2020, asymptomatic patient screening was implemented in these dialysis centres. Quantitative real time PCR (RT-PCR) assays of nasopharyngeal swabs were utilised for detection of SARS-CoV-2. For the outpatients, laboratory data were collected at the satellite HD unit on the date of the positive swab test (RT-PCR) for SARS-CoV-2.

Demographics and clinical and laboratory data were obtained retrospectively from electronic medical records, and follow-up was performed until 26th May, 2020.

(Six patients were recruited to the RECOVERY clinical trial. Four patients received standard supportive care, one received dexamethasone and one Lopinavir/Ritonavir therapy. The rest of the patients received standard care.)

Study parameters

Retrospective data regarding patients were obtained from the electronic medical records and included; date of birth, gender, ethnicity, deprivation index, body mass index (BMI), co-morbidities, clinical frailty score, dialysis access, regular medication, clinical presentation, observations, investigations.

The pre-admission frailty score was determined using the Rockwood Clinical Frailty Scale, a global clinical measure of fitness and frailty of an adult [10], that NICE guidelines recommend using as part of the holistic assessment for all adults admitted to hospital, irrespective of their COVID-19 status [11].

The English Index of Deprivation was determined based on the postcode of the home address and data were obtained from the official government website [12].

Self-reported symptoms were clustered into fever, respiratory, systemic and gastrointestinal systems. Respiratory symptoms included cough, sputum production, sore throat, expiratory wheeze and the presence of chest pain. Systemic manifestations included myalgia, joint pain, fatigue, generalised weakness and lethargy. Abdominal pain, vomiting and diarrhoea were presentations of the gastrointestinal cluster. The National Early Warning Score 2 (NEWS2), a scoring system widely utilised in the National Health Service (NHS) to standardise the assessment of patients with risk of clinical deterioration [13], has also been endorsed for use when managing patients with COVID-19. It is calculated for every patient admitted to hospital.

Laboratory tests included full blood count, ferritin, C-reactive protein (CRP), liver function test, creatinine kinase (CK), lactate dehydrogenase (LDH), brain natriuretic peptide (BNP), troponin, clotting screen and D-dimer.

Outcomes

The primary outcome was the overall rate of death following COVID-19 diagnosis. Follow-up period was right censored on 26th May, 2020. Secondary outcome included the need for hospital admission.

Statistical analysis

Normality of data distribution was assessed using the Shapiro–Wilk test. Two-group comparisons for quantitative parameters were made with Student's t test, Welch's t test or Mann–Whitney U test, as appropriate. Comparisons between more than two groups for quantitative parameters were made with Analysis of Variance (ANOVA) and Kruskal–Wallis test. Chi squared test or Fisher's exact test was used for comparing groups with qualitative parameters. Kaplan–Meier curves and the log-rank test were used for the assessment and comparison of survival among patient groups. Multivariable logistic regression analysis was used to assess the parameters that were independently associated with the need of admission and death. All the tests were two-tailed. Results were considered statistically significant if p value was less than 0.05. Statistical analysis was performed using the 25th edition of Statistical Package for Social Sciences (SPSS) (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics, clinical presentation and diagnostic finding

Demographic data, comorbidities and medical history of all patients are described in Table 1.

Of the 746 patients undergoing haemodialysis at our four dialysis units, 164 (22%) tested positive for SARS-CoV-2. We excluded 11 asymptomatic patients that were identified on routine sampling as well as five patients who acquired COVID-19 infection during an inpatient admission for other illnesses. The remaining 148 symptomatic COVID-19 positive patients were analysed in detail.

The mean of age was 64.1 ± 14.6 years. Male gender (56.8%) and black ethnicity (38.5%) were more prevalent in this HD population. The most common comorbidities were hypertension (82.4%), chronic cardiac disease (54.7%) and diabetes (52.7%) and the median BMI was 27.75 (IQR 22.93–33.2). The median Rockwood Clinical Frailty Scale was 5 (IQR 4–6). Patients had a median 45 (IQR 17–55) days of follow-up.

Clinical presentations and detailed observations are reported in Table 2. Most patients had respiratory and systemic cluster symptoms (77.1% and 60.2%, respectively). The average NEWS2 Score on admission was 4.03 ± 2.67. The median lymphocyte, neutrophil, neutrophil-to-lymphocyte count (NLR) and CRP at presentation was 0.81 (0.50–1.14), 4.36 (3.0–5.9), 5.60 (3.54–8.32) and 52.0 (26.0–133.3), respectively. Bilateral opacities were found in 60.4% of chest X-rays.

Clinical outcomes

Mortality

Ninety-three/148 patients (62.8%) required hospital admission and 10 of them (6.8%) were admitted to intensive care. Thirty-six patients died (overall mortality rate 24.3%). On the last day of follow-up one patient remained hospitalised.

In the univariate analysis, comparing those that died with those that survived, we observed that the deceased patients were older compared to the survivors (mean age 71.7 years ± 11.9 vs. 61.7 ± 14.6 years, respectively, $p = 0.0003$), frailer [median frailty score: 6 (5–6) vs. 5 (3–6), $p = 0.0002$] and had more ischaemic heart disease (50% vs. 22.3%, $p = 0.0027$). Those who died had a lower BMI compared to survivors [median 24.95 (20.35–30.65) vs. 28.55 (23.23–34.38); $p = 0.0232$]. Neither ethnicity

nor index of multiple deprivation differed significantly between survivors and non-survivors in this cohort.

Self-reported fever symptoms were described in 55.3% of all patients and were more frequent in those who survived (61.2% vs. 38.2%, $p = 0.0274$), however, measured temperature was not different between the groups. Despite similar initial NEWS2 scores between the groups, those who died presented with lower systolic blood pressure compared to survivors (130.7 ± 33.4 vs. 146.7 ± 31.1 mmHg, $p = 0.0207$).

Deceased patients had higher total white blood cell count (WBC), neutrophils and NLR when compared to survivors (Table 3). Inflammatory markers were also higher in non-survivors, including CRP (128 vs. 40.5 mg/L; $p < 0.0001$) and ferritin (1,691 vs. 1,004 μg/L; $p = 0.0335$). Significantly, lower albumin and higher bilirubin were found in deceased patients when compared to survivors (31.9 vs. 35.9 g/L; $p < 0.0001$ and 6.0 vs. 5.0 μmol/L; $p = 0.0171$, respectively). Troponin was also associated with mortality, showing higher values in those who died (198 vs. 113 ng/L, $p = 0.0034$).

Eleven asymptomatic patients with limited laboratory data were excluded from the analysis. After 3 months of follow-up from the date of their positive test, none had been admitted to hospital or died.

Hospitalisation

Out of 148 patients, 93 (62.8%) required hospital admission. The median length of stay was 9.0 days (IQR 5.0–14.0).

During hospitalisation, 71 (76.3%) of 93 inpatients received non-invasive respiratory support via non-rebreathing oxygen face mask or nasal cannula, 1 (1.1%) via high-flow nasal cannula, 2 (2.1%) via non-invasive ventilation (pressurised oxygen) and 7 (7.53%) were mechanically ventilated. Ten patients were admitted to intensive care and had a median stay of 10.5 (IQR 2.8–32.5) days. At the end of follow-up, only one patient remained in hospital.

In the univariate analysis, those who were hospitalised were older (66.84 years ± 14.6 vs. 59.55 ± 13.5, $p = 0.0031$), a higher proportion had a higher frailty score (despite the same median 5 (4–6) vs. 5 (3–6), $p = 0.0236$), and laboratory tests demonstrated higher levels of median NLR (6.6 (4.2–9) vs. 3.9 (2–5.8), $p < 0.001$) and CRP [85 (12.5–157.5) vs. 33 (6–60) mg/dL, $p < 0.001$].

None of the asymptomatic patients were admitted to hospital within the 3 months of follow-up from the date of the positive COVID test.

Multivariable analysis

We performed multivariable logistic regression for mortality and need for hospital admission and incorporated the following variables: age, gender, ethnicity, BMI, frailty score, deprivation index, type of vascular access, co-morbidities

Table 1 Baseline demographics and clinical characteristics of HD patients

	All $n=148$	Outcome: death			Outcome: hospital admission		
		Non-survivors $n=36$	Survivors $n=112$	P value	Inpatients $N=93$	Outpatients $n=55$	P value
Age (years) (mean ± SD)	64.13 ± 14.6	71.69 ± 11.9	61.70 ± 14.6	0.0003	66.84 ± 14.6	59.55 ± 13.5	**0.0031**
Male sex, n (%)	84 (56.8%)	24 (66.7%)	60 (53.6%)	0.1818	54 (58.1%)	30 (54.5%)	0.7326
Ethnicity, n (%)				0.4890			0.5182
White	48 (32.4%)	14 (38.9%)	34 (30.3%)		33 (35.5%)	15 (27.3%)	
Black	57 (38.5%)	11 (30.5%)	46 (41.1%)		33 (35.5%)	24 (43.6%)	
Asian and others	43 (29.1%)	11 (30.5%)	32 (28.6%)		27 (29.0%)	16 (29.1%)	
Index of multiple deprivation rank (median (IQR))	9676 (4760–15,642)	8533 (5530–17,114)	9851 (4727–15,642)	0.7665	9462 (4773–15,353)	9954 (4720–15,900)	0.8969
Index of multiple deprivation decile (median (IQR))	3.0 (2.0–5.0)	3.0 (2.0–5.8)	3.5 (2.0–5.0)	0.6579	3.0 (2.0–5.0)	4.0 (2.0–5.0)	0.9099
BMI (kg/m^2) (median (IQR))	27.75 (22.93–33.20)	24.95 (20.35–30.65)	28.55 (23.23–34.38)	0.0232	26.90 (22.3–32.2)	28.40 (23.1–34.8)	0.2205
Co-morbidities							
Diabetes, n (%)	78 (52.7%)	20 (55.6%)	58 (51.8%)	0.7064	53 (57%)	25 (45.5%)	0.2330
Hypertension, n (%)	122 (82.4%)	31 (86.1%)	91 (81.3%)	0.6195	77 (82.8%)	45 (81.8%)	>0.9999
Ischemic heart disease, n (%)	43 (29.1%)	18 (50%)	25 (22.3%)	0.0027	31 (33.3%)	12 (21.8%)	0.1894
Chronic cardiac disease, n (%)	81 (54.7%)	21 (58.3%)	60 (53.6%)	0.7017	48 (51.6%)	33 (60%)	0.3934
Chronic pulmonary disease, n (%)	19 (12.8%)	8 (22.2%)	11 (9.8%)	0.0818	15 (16.1%)	4 (7.3%)	0.1357
HIV, n (%)	6 (4.1%)	3 (8.3%)	3 (2.7%)	0.1572	6 (6.5%)	0	0.0846
Clinical Frailty Score (median (IQR))	5 (4–6)	6 (5–6)	5 (3–6)	0.0002	5 (4–6)	5 (3–6)	**0.0236**
Dialysis access – Line, n (%)	47 (31.8%)	13 (36.1%)	34 (30.4%)	0.5414	31 (33.3%)	16 (29.1%)	0.7152
Medications							
ACEI/ ARB, n (%)	22 (15.0%)	7 (19.4%)	15 (13.5%)	0.4230	17 (18.5%)	5 (9.1%)	0.1544
Statin, n (%)	96 (65.3%)	25 (69.4%)	71 (64.0%)	0.6875	61 (66.3%)	35 (63.6%)	0.8581
Anti-platelet agent, n (%)	71 (48.0%)	23 (63.9%)	48 (42.9%)	0.0351	46 (49.5%)	25 (45.5%)	0.7339
NOAC/ warfarin, n (%)	9 (6.1%)	2 (5.6%)	7 (6.3%)	>0.9999	5 (5.4%)	4 (7.3%)	0.7270
Prednisone, n (%)	13 (8.8%)	5 (13.9%)	8 (7.1%)	0.3064	11 (11.8%)	2 (3.6%)	0.1325
Tacrolimus/ Cyclosporine, n (%)	9 (6.1%)	1 (2.8%)	8 (7.1%)	0.6885	4 (4.3%)	5 (9.1%)	0.2931
Immunosuppressive treatment, n (%)	18 (12.2%)	6 (16.7%)	12 (10.7%)	0.3818	12 (12.9%)	6 (10.9%)	0.7996

Bold means p-value < 0.05

Table 2 Clinical picture and observation at initial presentation of COVID-19 infection in HD patients

	All $n = 148$	Non-survivors $n = 36$	Survivors $n = 112$	P value
Clinical presentation				
Fever, n (%) $n = 132$	73 (55.3%)	13 (38.2%)	60 (61.2%)	**0.0274**
Respiratory symptoms, n (%) $n = 131$	101 (77.1%)	28 (82.3%)	73 (75.3%)	0.4820
Systemic symptoms, n (%) $n = 128$	77 (60.2%)	23 (67.7%)	54 (57.4%)	0.3162
GI symptoms, n (%) $n = 126$	37 (29.4%)	11 (32.3%)	26 (28.3%)	0.6645
Observation				
Temperature (°C) (median (IQR))	37.10 (36.1–42.0)	37.15 (36.7–38.0)	37.10 (36.7–37.8)	0.8047
Heart rate (beats/min) (mean ± SD)	88.28 ± 17.4	87.97 ± 15.8	88.45 ± 18.3	0.8976
Systolic blood pressure (mmHg) (mean ± SD)	141.1 ± 32.64	130.7 ± 33.4	146.7 ± 31.1	**0.0207**
Diastolic blood pressure (mmHg) (mean ± SD)	73.99 ± 19.11	72.35 ± 22.5	74.87 ± 17.1	0.5382
Respiratory rate (/min) (median (IQR))	22 (20–24)	21 (20–28)	22 (20–24)	0.9852
Oxygen saturation (%) (median (IQR))	97 (95–98)	96.0 (94.5–98.0)	97.0 (95.5–98.0)	0.4869
Oxygen saturation with supplementary O_2 (%) (median (IQR))	97 (94–100)	98 (94.5–100)	97.0 (94.0–98.0)	0.2559
O2 liter (median (IQR))	4.0 (2.5–15)	4.5 (4–15)	4.0 (2–15)	0.4587
NEWS2 Score (mean ± SD)	4.03 ± 2.67	4.44 ± 2.96	3.79 ± 2.48	0.2627
Chest X Ray, n (%). ($n = 106$)				0.8119
Bilateral opacities	61 (60.4%)	22 (64.7%)	39 (58.2%)	
Unilateral opacities	16 (15.8%)	5 (14.7%)	11 (16.4%)	
No opacities	24 (23.8%)	7 (20.6%)	17 (25.4%)	
Hospital admission, n (%)	93 (62.8%)	34 (94.4%)	59 (52.7%)	**< 0.0001**
Length of hospital stay (days) (median (IQR))	9.0 (5.0–14.0)	8.5 (5.8–12.5)	9.0 (5.0–16.2)	0.8482
ICU stay, n (%)	10 (6.8%)	5 (13.9%)	5 (4.5%)	0.0636

Bold means p-value < 0.05

Table 3 Laboratory tests at initial presentation of COVID-19 infection in HD patients

	All $n = 148$	Non-survivors $n = 36$	Survivors $n = 112$	P value
Hb (g/L) (mean ± SD)	107.2 ± 15.6	109.3 ± 16.4	106.5 ± 15.4	0.3547
RDW (median (IQR))	16.2 (15.1–17.2)	16.1 (14.8–17.7)	16.2 (15.1–17.2)	0.8164
WBC (× 10^9/L) (median (IQR))	5.90 (4.2–7.7)	7.45 (5.6–9.8)	5.40 (4–7)	**0.0007**
Platelets (× 10^9/L) (median (IQR))	171.0 (144–219)	171.0 (124.8–224.0)	171.0 (147.0–219.0)	0.4174
Neutrophils (× 10^9/L) (median (IQR))	4.36 (3.0–5.9)	6.00 (4.3–7.1)	3.80 (2.9–5.4)	**< 0.0001**
Lymphocyte (× 10^9/L) (median (IQR))	0.81 (0.50–1.14)	0.64 (0.34–1.09)	0.84 (0.6–1.2)	0.0603
Neutrophil to lymphocyte ratio (median (IQR))	5.60 (3.54–8.32)	7.32 (4.9–20.0)	5.18 (3.1–7.5)	**0.0015**
Ferritin (µg/L) (median (IQR))	1125 (741–2289)	1691 (935–2845)	1004 (645–1857)	**0.0335**
CRP (mg/L) (median (IQR))	52.0 (26.0–133.3)	128.0 (75.0–261.8)	40.5 (23.0–108.8)	**< 0.0001**
Albumin (g/L) (mean ± SD))	34.81 ± 4.7	31.89 ± 4.7	35.90 ± 4.3	**< 0.0001**
ALT (unit/L) (median (IQR))	25.0 (19–38)	22.0 (18–43.5)	25 (19–34.8)	0.9296
Bilirubin (µmol/L) (median (IQR))	6.00 (4.0–7.8)	6.00 (5.0–10.0)	5.00 (4.0–7.0)	**0.0171**
AST (unit/L) (median (IQR))	35.0 (27–55)	41.0 (29–52)	34.5 (25–58)	0.3615
CK (unit/L) (median (IQR))	167 (64.0–387.5)	159.5 (57.5–303.8)	167.0 (69.0–410.0)	0.8346
LDH (unit/L) (median (IQR))	338.0 (261.3–445.8)	308.5 (237.8–515.5)	353.5 (271.0–432.3)	0.7603
NT-BNP (ng/L) (median (IQR))	6530 (3348–28,256)	27,852 (3367–28,643)	5700 (3289–18,448)	0.3015
Troponin (ng/L) (median (IQR))	135 (79.8–211.3)	198 (107–317)	113 (74–164)	**0.0034**
INR (ratio) (median (IQR))	1.10 (1.0–1.1)	1.10 (1.0–1.2)	1.10 (1.0–1.1)	0.5703
APTT (seconds) (median (IQR))	39.1 (35.1–45.3)	39.8 (36.3–55.4)	38.4 (34.3–44.3)	0.2003
Fibrinogen (g/L) (mean ± SD)	5.27 ± 1.1	5.2 ± 1.0	5.3 ± 1.2	0.7255
D-dimer (ng/mL) (median (IQR))	1685 (1079–2643)	1685 (1030–2362)	1658 (1106–2821)	0.8830

Bold means p-value < 0.05

(diabetes, hypertension, chronic cardiac and pulmonary disease), use of immunosuppression and biomarkers including CRP and NLR (Table 4). With these models we found that only older age and higher CRP are predictors of mortality, while higher NLR and CRP are prognostic factors for hospital admission.

Discussion

In a large urban renal unit, 22% of patients undergoing in-centre haemodialysis developed confirmed COVID-19 during the height of the London pandemic. Over 60% were hospitalised and 24% died. Factors associated with death included older age, higher frailty scores, a history of ischaemic heart disease, and surprisingly a lower BMI. In addition, a number of laboratory tests mostly reflecting greater degrees of inflammation were also associated with mortality. Factors associated with hospitalisation were similar, a higher frailty score, advanced age and markers reflecting systemic inflammation. Our study was a retrospective analysis and was relatively modest in size, with only 36 deaths,

potentially explaining why other factors previously highlighted as being risk factors for death from COVID-19 in the general population were not demonstrable. In one of the largest global epidemiology studies involving data from over 17.4 million UK adult patients, older age, male sex, social deprivation and Black as well as Asian ethnicity were identified as strong risk factors for death due to COVID-19 disease [14] Older age is also mentioned as a risk factor for mortality in a study from China published at the beginning of the pandemic [15].

In another large UK-based study, ISARIC WHO CCP-UK, which featured over 20,000 patients admitted to hospital, increasing age, male sex, and chronic co-morbidities including obesity were independent risk factors for increased mortality. The median age of patients was 73 years, the commonest co-morbidities were chronic cardiac disease (31%) and diabetes (21%), and the mortality rate was 26% in this cohort [16].

However, there is a paucity of identified risk factors portending poor outcome in haemodialysis patients with COVID-19. We found no effect of age, gender, ethnicity, history of diabetes or hypertension on mortality, but this is

Table 4 Multivariable analysis for death and hospital admission in hemodialysis patients with COVID-19

Variables	Outcome: death		Outcome: hospital admission	
	Multivariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.05 (1.00–1.10)	**0.044**	1.03 (0.99–1.07)	0.167
Gender (Male as reference)				
Female	0.68 (0.23–1.96)	0.471	0.84 (0.34–2.09)	0.710
Ethnicity (White as reference)		0.857		0.658
Black	1.12 (0.30–4.14)	0.864	1.53 (0.48–4.82)	0.470
Asian	0.78 (0.22–2.79)	0.701	0.98 (0.28–3.42)	0.978
Body mass index	0.94 (0.87–1.01)	0.100	0.96 (0.90–1.03)	0.263
Frailty score	1.50 (0.97–2.32)	0.069	0.98 (0.66–1.43)	0.896
Deprivation index (deciles)	1.05 (0.82–1.35)	0.695	1.08 (0.86–1.36)	0.508
Vascular access (AVF/AVG as reference)				
Central venous line	1.37 (0.43–4.36)	0.593	1.67 (0.60–4.59)	0.324
Diabetes (No as reference)				
Yes	2.20 (0.64–7.49)	0.209	2.16 (0.73–6.34)	0.162
Hypertension (No as reference)				
Yes	3.58 (0.57–22.69)	0.175	0.94 (0.26–3.42)	0.925
Cardiac disease (No as reference)				
Yes	0.77 (0.26–2.25)	0.626	0.61 (0.25–1.47)	0.269
Pulmonary disease (No as reference)				
Yes	1.01 (0.21–4.75)	0.067	1.70 (0.34–8.39)	0.514
Immunosuppression (No as reference)				
Yes	4.12 (0.91–18.74)	0.067	1.06 (0.25–4.50)	0.933
Neutrophil to lymphocyte ratio	1.04 (0.99–1.09)	0.125	1.20 (1.01–1.42)	**0.037**
C-reactive protein	1.01 (1.01–1.02)	**<0.001**	1.01 (1.00–1.02)	**0.002**

Bold means p-value < 0.05

most likely due to the small numbers. Moreover, in univariate analysis, patients in our HD cohort with higher BMI had better outcomes (from COVID-19) compared to those with lower BMI. This is possibly due to underlying sub-nutrition in the lower BMI group, however, previous data have shown that obesity is associated with reduced mortality in HD patients, unlike the general population, suggesting that adiposity may be involved in a different pathophysiological way in HD patients [17] We found no relationship between BMI and inflammatory markers such as CRP, but nonetheless BMI was not associated with outcome by multivariate analysis.

Our findings are consistent with, and expand on, recent data from haemodialysis centres in North-West London which showed that increased age and inflammatory markers were risk factors for death and hospitalisation in similar sized cohorts [18] Again Black Asian Minority ethnic (BAME) ethnicity and diabetes were not associated with admission or death.

Similarly, no association between severity of COVID-19 disease or mortality was found with diabetes, coronary heart disease and obesity in small haemodialysis cohorts from China and Spain [19, 20] or from larger London cohorts [5]. In addition, although 56.7% of our patients were from a BAME background, we did not demonstrate a mortality difference in these groups compared with other ethnicities, which is in accordance with the observation from other London-based dialysis units [5].

Our calculated mortality rate in HD patients with COVID-19 was higher than the current mortality rate in the general population (24.3% vs. 12%) and is in keeping with other recent reports from larger HD cohorts.

Compared to other haemodialysis cohorts, the incidence of COVID-19 among patients from the four satellite HD units based in northern London (22%) was similar to what was observed in HD from another London unit (19.6%) [5]. However, these incidences were slightly higher than what was seen in chronic HD patients from Italy (15%) [9] and China (2–18%) [19, 21, 22].

Our rate of hospitalisation is comparable to that in other studies of haemodialysis cohorts (62.8% vs. 61%) [9]. Our mortality rate however is slightly lower with 24.3% compared to studies from Italy (29%) [9], Spain (30.5%) [20] and New York (31%) [6]. These differences might be influenced by the difference in demographics as well as by the medical practice and threshold of escalation of care to intensive care unit in each country. However, these data clearly refute the idea that HD patients have mild disease or are in any way protected from the significant inflammation induced during COVID-19.

We demonstrated that advanced age is a marker for poor clinical outcome of COVID-19 disease in the haemodialysis population. Our study also highlighted an association between high CRP with both mortality and the need for hospital admission, which was also demonstrated in other studies [9, 20] Elevated levels of CRP have been shown to be a potential early marker of severity of COVID-19 disease [23–26] and other viral infections, although they lack specificity [27, 28] Moreover, we showed that higher neutrophil counts and lower lymphocyte levels are associated with higher mortality possibly due to bacterial co-infection and higher viral load [29, 30]. The risk factors that we found in our analysis are non-modifiable, and therefore one might consider the usefulness of these risk factors when assessing and counselling patients.

We also do not know the exact denominator of those who are positive for SARS-Cov-2 testing to determine the case fatality rate in our cohort, as testing of asymptomatic patients was only introduced a month after the first patient in our haemodialysis cohort was identified as positive.

Under the pressure of the COVID-19 epidemic it is important to both identify the risk factors that can predict poor outcome in preparation for future waves, and to stratify the use of therapeutic interventions that have been identified in recent trials in patients with preserved renal function in an attempt to decrease mortality and hospitalisation in this highly vulnerable group.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was approved by NHS ethics committee 20/SW/0077.

Consent to participate Not applicable.

Consent for publication Not applicable.

Reference

1. Zhou P, Lou YX, Wang XG et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 12:56–134

2. Wu F, Zhao S, Yu B et al (2020) A new coronavirus associated with human respiratory disease in China. Nature 579(7798):265–269

3. WHO Coronavirus Disease (COVID-19) Dashboard WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. Available from: https://covid19.who.int/?gclid=CjwKCAjw9vn4BRBaEiwAh0muDFyDES_ke8YAnjX504jqNYq5x7IkALU3tUDncoxz_xMN9mTQoxSSLxoCoGYQAvD_BwE. (Accessed date 2020 Jul 27)

4. [Withdrawn] [Withdrawn] Guidance on social distancing for everyone in the UK–GOV.UK [Internet]. Available from: https://www.gov.uk/government/publications/covid-19-guidance-on-social-distancing-and-for-vulnerable-people/guidance-on-social-distancing-for-everyone-in-the-uk-and-protecting-older-people-and-vulnerable-adults. (Accessed date 2020 Jul 27)

5. Corbett RW, Blakey S, Nitsch D et al (2020) Epidemiology of COVID-19 in an urban dialysis center. J Am Soc Nephrol JASN 31(8):1815–1823

6. Valeri AM, Robbins-Juarez SY, Stevens JS et al (2020) Presentation and outcomes of patients with ESKD and COVID-19. J Am Soc Nephrol 10:19–23

7. Fisher M, Mokrzycki MH, Coco M (2020) Chronic hemodialysis patients hospitalized with COVID-19 – short-term outcomes in bronx New York. Kidney 1:273–278

8. Sánchez-Álvarez JE, Fontán MP, Martín CJ et al (2020) Status of SARS-CoV-2 infection in patients on renal replacement therapy. Report of the COVID-19 Registry of the Spanish Society of Nephrology (SEN). Nefrología (English Edition) 10:23–45

9. Alberici F, Delbarba E, Manenti C et al (2020) 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. Kidney Internat 10:24–65

10. Rockwood K, Song X, MacKnight C et al (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ 173(5):489–495

11. National Institure for Health and Care Excellence (2020) COVID-19 rapid guideline : critical care. NICE Guidline 9:109–343

12. English indices of deprivation 2019: Postcode Lookup [Internet]. Available from: http://imd-by-postcode.opendatacommunities.org/imd/2019. (Accessed date 2020 Jul 27)

13. Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. [Internet]. 2017. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

14. Williamson EJ, Walker AJ, Bhaskaran K et al (2020) OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature 17:120–134

15. Zhou F, Yu T, Du R et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 5:19

16. Docherty AB, Harrison EM, Green CA et al (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ 369:m1985

17. Park J, Ahmadi SF, Streja E et al (2014) Obesity paradox in end-stage kidney disease patients. Prog Cardiovas Dis 56(4):415–425

18. Medjeral-Thomas NR, Thomson T, Ashby D, Muthusamy A, Nevin M, Duncan N, Loucaidou M, for the ICHNTRC group, (2020) Cohort study of outpatient hemodialysis management strategies for COVID-19 in North-West London. Kidney Internat Rep 5(11):2055–2065

19. Xiong F, Tang H, Liu L et al (2020) Clinical characteristics of and medical interventions for COVID-19 in hemodialysis patients in Wuhan China. J Am Soc Nephrol 10:2020030354

20. Goicoechea M, Sánchez Cámara LA, Macías N et al (2020) COVID-19: clinical course and outcomes of 36 maintenance hemodialysis patients from a single center in Spain. Kidney Internat 98(1):27–34

21. Ma Y, Diao B, Lv X et al (2020) 2019 novel coronavirus disease in hemodialysis (HD) patients: report from one HD center in Wuhan China. medRxiv 02(24):20027201

22. Tang H, Tian J, Dong J et al (2020) Serologic detection of SARS-CoV-2 infections in HD centers population. Am J Kidney Dis 76(4):490–499

23. Ali N (2020) Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol 10:170–183

24. Wang L (2020) C-reactive protein levels in the early stage of COVID-19. Med Maladies Infect 13:120–134

25. Li H, Xiang X, Ren H et al (2020) SAA is a biomarker to distinguish the severity and prognosis of Coronavirus Disease 2019 (COVID-19). J infect 10:18

26. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A (2020) The role of biomarkers in diagnosis of COVID-19 – a systematic review. Life Sci 1:10

27. Zimmerman O, Rogowski O, Aviram G et al (2010) C-reactive protein serum levels as an early predictor of outcome in patients with pandemic H1N1 influenza A virus infection. BMC Infect Dis 10(1):288

28. Durán A, González A, Delgado L, Mosquera J, Valero N (2016) Serum level of C-reactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. J Med Virol 88(2):351–355

29. Liu Y, Du X, Chen J et al (2020) Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 1:15

30. Yang AP, Ping LJ, Qiang TW, Ming LH (2020) The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Internat Immunopharmacol 13:106504