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ORIGINAL ARTICLE

Clinical triage of patients on kidney replacement therapy presenting with COVID-19: an ERACODA registry analysis

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ABSTRACT

Background. Patients on kidney replacement therapy (KRT) are at very high risk of coronavirus disease 2019 (COVID-19). The triage pathway for KRT patients presenting to hospitals with varying severity of COVID-19 illness remains ill-defined. We studied the clinical characteristics of patients at initial and subsequent hospital presentations and the impact on patient outcomes.

Methods. The European Renal Association COVID-19 Database (ERACODA) was analysed for clinical and laboratory features of 1423 KRT patients with COVID-19 either hospitalized or non-hospitalized at initial triage and those re-presenting a second time. Predictors of outcomes (hospitalization, 28-day mortality) were then determined for all those not hospitalized at initial triage.

Results. Among 1423 KRT patients with COVID-19 [haemodialysis (HD), $n = 1017$; transplant, $n = 406$), 25% ($n = 355$) were not hospitalized at first presentation due to mild illness (30% HD, 13% transplant). Of the non-hospitalized patients, only 10% ($n = 36$) re-presented a second time, with a 5-day median interval between the two presentations (interquartile range 2–7 days). Patients who re-presented had worsening respiratory symptoms, a decrease in oxygen saturation (97% versus 90%) and an increase in C-reactive protein (26 versus 73 mg/L) and were older (72 vs 63 years) compared with those who did not return a second time. The 28-day mortality between early admission (at first presentation) and deferred admission (at second presentation) was not significantly different (29% versus 25%; P = 0.6). Older age, prior smoking history, higher clinical frailty score and self-reported shortness of breath at first presentation were identified as risk predictors of mortality when re-presenting after discharge at initial triage.

Conclusions. This study provides evidence that KRT patients with COVID-19 and mild illness can be managed effectively with supported outpatient care and with vigilance of respiratory symptoms, especially in those with risk factors for poor outcomes. Our findings support a risk-stratified clinical approach to admissions and discharges of KRT patients presenting with COVID-19 to aid clinical triage and optimize resource utilization during the ongoing pandemic.

Keywords: COVID-19, dialysis, kidney, mortality, second presentation, transplantation

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has caused devastation to human lives and major disruptions of healthcare systems around the world. Patients with advanced chronic kidney disease (CKD) on kidney replacement therapy (KRT) with dialysis or transplantation have been identified as specifically vulnerable groups [1]. If infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), these patients often require admission, high-intensity in-patient care and major utilization of hospital resources. However, the optimal care pathway for KRT patients presenting with varying severity of COVID-19 was not well defined.

While 80% of patients with COVID-19 have mild symptoms, ~10–20% of patients can develop severe disease [2].

KEY LEARNING POINTS

What is already known about this subject?

- The clinical triage pathway for kidney replacement therapy (KRT) patients presenting with coronavirus disease 2019 (COVID-19) illness of varying severity has not been well defined. In the current phase of the pandemic, kidney patients are at high risk and present with varying degrees of severity. The ongoing pandemic has placed a major strain on hospital resources and clinical pathways, affecting overall care. The European Renal Association COVID-19 Database is a comprehensive pan-European multicentre registry with prospective data collection on COVID-19.

What this study adds?

- This study focuses specifically on patients who were not admitted on initial presentation but re-presented to hospitals a second time and compares clinical characteristics and outcomes of hospitalization and 28-day mortality with other cohorts. Such a large, multicentre dataset on this topic has not been presented to our knowledge.
- The study informs the outcome predictors for those admitted on second presentation and their clinical characteristics, indicating how to clinically risk stratify kidney patients safely on initial triage. This provides evidence, reassurance for clinicians and clinical practice parameters on the basis of which such patients with varying COVID-19 severity can be managed when presenting to hospitals.

What impact this may have on practice or policy?

- This study will help in attaining optimal hospital resource utilization for COVID-19 and also create capacity for treating non-COVID-related illness in kidney patients. This is impoortant information from COVID-19 Wave 1 and such knowledge transfer will support the restoration plan for renal services.

Understanding the factors associated with progression of symptoms from the asymptomatic stage through to severe illness is essential for developing efficient and appropriate clinical triage systems. Avoidance of unnecessary hospitalizations, when clinically appropriate and safe, will offer protection for COVID-19 patients from potential exposure to hospital-acquired infections, minimize the risk of transmitting COVID-19 infections to others, allow continuation of standard and routine care, cause less disruption to patient lives and avoid overwhelming the healthcare system. There is limited information on risk factors that precipitate the need for hospital admission, worsening of symptoms following discharge and readmission outcomes in KRT patients with COVID-19. Characteristics and outcomes of patients with mild–moderate disease who are not hospitalized have been scarcely reported in the literature [3]. As the pandemic is sustained through a second and possible future waves, with a simultaneous increase in identification rates from enhanced testing and continued disruption of routine care, we urgently need to establish optimum triage tools to support decision making on hospitalization of KRT patients affected by COVID-19.

We analysed the data of patients receiving KRT who presented with COVID-19. Clinical features, laboratory results and outcomes of hospitalized and non-hospitalized patients at first presentation were studied and compared with characteristics of patients who returned for a second assessment. In addition, we identified predictors of subsequent admission and poor outcomes in those not admitted at their initial presentation.

MATERIALS AND METHODS

Study design and participants

This observational study used data from the European Renal Association COVID-19 Database (ERACODA), which was established in March 2020 [4]. This initiative is endorsed by the European Renal Association–European Dialysis and Transplantation Association (ERA-EDTA) and currently involves the cooperation of >200 physicians representing 130 centres in 31 countries, mostly in Europe and bordering the Mediterranean Sea. Data were collected on adult (≥18 years of age) patients with kidney failure treated with either long-term dialysis or a functioning kidney allograft. Patients were diagnosed with COVID-19 illness based on a positive result on a real-time reverse transcription polymerase chain reaction assay of nasal or pharyngeal swab specimens and/or compatible findings on computed tomography (CT) scan of the lungs. Data were gathered from outpatients as well as hospitalized patients. Physicians responsible for the care of these patients registered detailed demographic and clinical data, including information pertaining to disease severity, treatment and outcomes.

The ERACODA is hosted at the University Medical Center Groningen, Groningen, The Netherlands. Data are recorded using REDCap software (Research Electronic Data Capture, Vanderbilt University Medical Center, Nashville, TN, USA) [4]. Patient-identifiable information was stripped from each record and data were stored pseudonymized. The study was approved by the Institutional Review Board of the University Medical Center Groningen, who deemed the collection and analysis of

data exempt from ethics review as per the Medical Research Involving Human Subjects Act (WMO).

Data collection

For the current study, all patients with a COVID-19 diagnosis between 1 February and 30 June 2020 with complete clinical datasets on hospitalizations and Day 28 outcomes were included in the analysis. Detailed information was collected on patient characteristics (including age, sex, race, frailty score, comorbidities, hospitalization and medication use) and COVID-19-related characteristics (reason for COVID-19 screening, presenting symptoms, vital signs and laboratory test results) at presentation. Frailty was assessed on a scale of 1–9 based on the Clinical Frailty Scale (CFS) [5]. The CFS uses clinical descriptors and pictographs to generate a frailty score for a patient, with a score of 1 representing very fit and a score of 9 representing a terminally ill patient. Comorbidities were recorded from patient records and obesity was defined as a body mass index (BMI) $\geq$30 kg/m^2. Information was also collected on practical and logistic considerations, which mainly referred to organizational and local infrastructure constraints. We kept the definition broad to tease out the proportion of patients where decision making for clinical triage was based on patient and disease characteristics alone.

Statistical analysis

First, we examined characteristics of hospitalized and non-hospitalized patients at their first and second presentations. Second, we assessed characteristics of patients who were not admitted to the hospital initially but presented a few days later. To assess the disease course, we compared characteristics of the first and second presentations of those patients who presented twice. Continuous data are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR) in case of a non-normal distribution. Categorical data are presented as percentages. Characteristics were compared between groups using Student's *t* test for continuous variables (Mann–Whitney *U* test for non-normally distributed data) and Pearson chi-square for categorical variables.

To examine 28-day mortality, cumulative survival probabilities were plotted on Kaplan–Meier curves and compared using logrank tests for three groups of patients: those hospitalized at the first visit, those not hospitalized at the first visit who did not return for a second visit and those not hospitalized at the first visit who returned for a second visit.

For those patients who were discharged after the first presentation, we identified predictors of 28-day mortality, hospitalization and second presentation using a backward elimination procedure. For 28-day mortality, this was done using Cox proportional hazards regression, whereas predictors for hospitalization and second presentation were identified using a Fine and Gray competing risk model to account for the competing risk of mortality [6]. Candidate predictors were selected in a two-stage process. First, candidate factors were selected based on clinical knowledge. These factors include age, sex, race/ethnicity, tobacco use, frailty score, X-ray finding, CT scan finding, obesity, diabetes, hypertension, lung disease, active malignancy, autoimmune disease, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) use, type of KRT (dialysis/transplant), COVID-19-related symptoms and vital signs, including cough, fever, shortness of breath, headache, diarrhoea, nausea/vomiting, temperature, oxygen saturation, respiration rate, pulse rate, lymphocyte count and C-reactive protein (CRP). Subsequently, each of these variables was examined in a univariable analysis and those with a P-value $<$0.1 were considered candidate predictors for the multivariable model. Those variables with a P-value $<$0.2 in the multivariable model were identified as predictors and were included in the final model [7, 8].

All analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA). A two-sided P-value $<$0.05 indicated statistical significance.

RESULTS

A total of 1596 patients on KRT presented for evaluation of COVID-19 symptoms between 1 February and 30 June 2020. After excluding patients with missing information on hospitalization ($n = 27$), 28-day clinical status ($n = 121$) or both ($n = 25$), 1423 patients were included for analysis. Of these patients, at first presentation, 1068 were hospitalized and 355 were not hospitalized. Among the 355 patients not hospitalized at first presentation, 36 patients returned for a second presentation and 34 of them were hospitalized (Figure 1).

Patient characteristics

The demographic and clinical characteristics of patients in the study are shown in Table 1. On average, patients were 64 years old and the majority were male (61%). A total of 406 (29%) patients were kidney transplant recipients and 1017 (71%) were dialysis patients [99% haemodialysis (HD) and 1% peritoneal dialysis (PD)]. From this cohort of 1423 patients, 355 patients (25%) were not admitted at first presentation [13% ($n = 53$) of kidney transplant patients and 30% ($n = 302$) of dialysis patients]. The gender distribution, age and frailty score of these 355 non-hospitalized patients were similar to those of patients who were hospitalized after their initial assessment. However, the non-hospitalized patients had lower CRP values (13 versus 38 mg/L) and less frequent pulmonary symptoms including cough (38% versus 58%) and shortness of breath (11% versus 44%) and fewer abnormalities on chest X-ray (9% versus 44%) or CT scan (6% versus 41%). X-ray was not performed in 74% of non-hospitalized and 39% of hospitalized patients and CT scan was not performed in 81% of non-hospitalized and 68% of hospitalized patients on their first presentation. The median duration of in-patient stays among those hospitalized was 15 days (IQR 9–23). Only five patients were discharged alive within 24 h of hospital admission.

Second presentation

Thirty-six of the 355 patients (10%) who were not hospitalized at their first assessment presented for a second time with clinical illness (Table 1). Of these 36 patients, the numbers of transplant and dialysis recipients were 8 (22%) and 28 (78%), respectively. Among the 355 patients who were not hospitalized

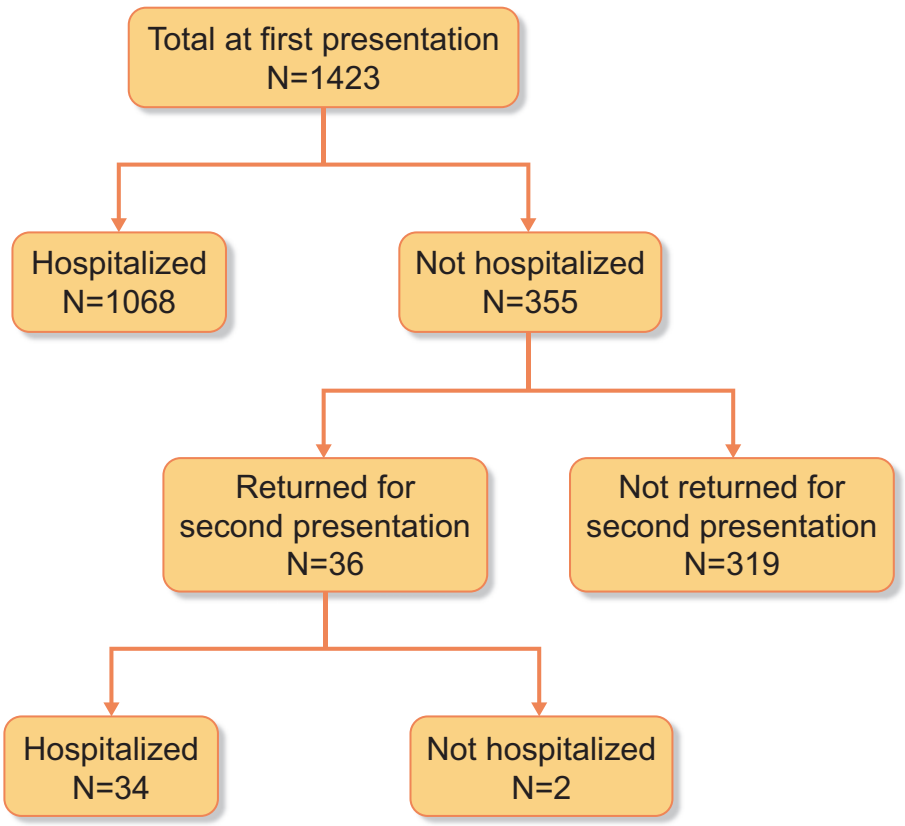

FIGURE 1: Flow chart for patient presentation and hospitalization.

initially, practical and logistical considerations precluded first hospital admission for 9% of patients who returned for a second assessment, compared with 1% of those who did not return (Supplementary data, Table S1). Supplementary data, Figure S1 shows the distribution of patients with a second presentation according to their country of residence. Second attendance cases were ≤5% of the reported cases in each country, except for France, where 24% of the reported cases returned for a second assessment (Supplementary data, Table S2). The median time interval between the first and second presentation was 5 days (IQR 2–7) (Supplementary data, Figure S2). Patients who presented a second time were older, more often had a history of prior tobacco use and more frequently had diabetic kidney disease compared with those who did not re-present at the hospital (Table 1). Furthermore, these patients more often had pulmonary symptoms including cough (56% versus 36%) and shortness of breath (22% versus 10%), abnormalities on chest X-ray (14% versus 8%), lower mean systolic blood pressure (129 ± 26 versus 139 ± 25 mmHg) and a higher median CRP value [26 mg/L (IQR 6–58) versus 12 (2–36)] on initial attendance compared with those patients who did not return for a second presentation.

Evolution of symptoms, vital signs and laboratory results from first hospital attendance to the second presentation

Patients who sought healthcare input for a second time had clinical symptoms characterized by worsening of respiratory illness, with cough, shortness of breath and a decline in their vital parameters, namely an increase in respiration rate, a decrease in blood oxygen saturation (from 97% to 90%) and an increase in pulse rate (from 73 to 78 bpm). Temperature and blood pressure did not change significantly between the first and second presentations (Table 2). An increase in CRP (from 26 to 73 mg/L) was also noted at the second presentation.

Comparison of characteristics of patients hospitalized at their first presentation and at baseline for those patients who returned for a second hospital episode

Compared with patients admitted after their initial consultation, those who were admitted later were older, more often had prior tobacco use and at the time of their initial assessment, less often had shortness of breath and fever, a lower respiratory rate, higher oxygen saturation, lower diastolic blood pressure and

Table 1. Characteristics of all patients at first presentation stratified according to their hospital admission status

Characteristics	Total ($N = 1423$)	Hospitalization at first presentation		P-value	Not hospitalized at first presentation ($n = 355$)		P-value
		Yes ($n = 1068$)	No ($n = 355$)		Returned for second presentation ($n = 36$)	Did not return for second presentation ($n = 319$)	
Sex (male), %	61	62	56	0.06	64	55	0.33
Age (years), mean ± SD	64 ± 15	64 ± 14	64 ± 16	0.53	72 ± 14	63 ± 16	0.002
BMI (kg/m^2), mean ± SD	27 ± 5	27 ± 5	27 ± 6	0.67	27 ± 4	27 ± 6	0.86
Race, %				0.05			0.93
Asian	3	3	4		6	4	
Black or African descent	6	5	7		9	7	
White or Caucasian	86	86	86		83	86	
Other or unknown	5	6	3		3	3	
Tobacco use, %				<0.001			0.001
Current	6	7	4		0	4	
Prior	22	22	19		42	17	
Never	45	47	39		42	39	
Unknown	28	24	37		17	40	
CFS (AU), mean ± SD	3.7 ± 1.8	3.7 ± 1.8	3.7 ± 1.7	0.74	3.9 ± 1.7	3.7 ± 1.8	0.44
Patient identification, %				<0.001			0.03
Symptoms only	73	75	66		85	64	
Symptoms and contact	14	15	11		15	10	
No symptoms but contact	5	5	6		0	6	
Routine screening	8	5	17		0	20	
COVID-19 test result, %							
Positive	94	92	97		92	98	
Negative	4	5	2		6	2	
Intermediate/unknown	2	2	1		3	–	
Abnormality on X-ray (yes), %	35	44	9	<0.001	14	8	0.03
Abnormality on CT scan (yes), %	32	41	6	<0.001	8	5	0.35
Comorbidities, %							
Obesity	23	23	21	0.45	15	22	0.34
Hypertension	83	83	84	0.79	83	84	0.95
Diabetes mellitus	39	40	39	0.62	44	38	0.45
Coronary artery disease	29	30	28	0.50	33	27	0.44
Heart failure	19	21	14	0.007	17	14	0.68
Chronic lung disease	12	12	11	0.55	17	11	0.28
Active malignancy	6	7	3	0.01	8	3	0.08
Autoimmune disease	5	5	4	0.31	8	3	0.11
Primary kidney disease, %							
Primary glomerulonephritis	16	16	13	0.12	14	13	0.81
Pyelonephritis	2	3	1	0.20	0	2	0.45
Interstitial nephritis	4	5	3	0.10	3	3	0.92
Hereditary kidney disease	10	10	12	0.24	9	12	0.53
Congenital diseases	2	2	3	0.26	0	3	0.28
Vascular diseases	13	12	14	0.47	17	14	0.55
Secondary glomerular disease	7	7	10	0.06	11	10	0.74
Diabetic kidney disease	21	22	19	0.27	34	17	0.02
Other	14	13	18	0.02	6	19	0.05
Unknown	10	11	8	0.09	6	8	0.63
Dialysis (yes), %	71	67	85	<0.001	78	86	0.19
HD[a]	99	99	99	0.29	100	99	0.57
PD[a]	1	1	1		0	1	
Residual diuresis ≥200 mL/day[a]	32	33	31	0.002	46	29	0.006
Transplant waiting list status[a], %				0.001			0.12
Active on waiting list	11	11	10		7	11	
In preparation	10	10	10		7	10	
Temporarily not on list	9	10	7		4	6	
Not transplantable	63	64	61		82	58	
Unknown	7	5	13		0	15	
Transplantation (yes), %	29	34	15		22	14	
Time since transplantation[b], %				0.12			0.04
<1 year	7	8	2		0	13	

Continued

Table 1. Continued

Characteristics	Total ($N = 1423$)	Hospitalization at first presentation		P-value	Not hospitalized at first presentation ($n = 355$)		P-value
		Yes ($n = 1068$)	No ($n = 355$)		Returned for second presentation ($n = 36$)	Did not return for second presentation ($n = 319$)	
1–5 years	32	31	42		50	40	
>5 years	61	61	57		38	60	
Medication, %							
ACE inhibitor use (yes)	16	17	14	0.32	19	11	0.007
ARB inhibitor use (yes)	16	15	19	0.12	22	15	0.014
Use of immunosuppressive medication, %							
Prednisone	85	86	84	0.61	92	82	0.41
Tacrolimus	67	67	66	0.83	67	66	0.97
Cyclosporine	10	11	7	0.45	0	8	0.31
Mycophenolate	58	58	55	0.63	50	56	0.68
Azathioprine	4	4	4	0.82	0	5	0.44
mTOR inhibitor	12	12	11	0.81	17	10	0.49
Disease characteristics							
Days from symptoms onset, median (IQR)	2 (0–4)	2 (0–5)	1 (0–3)	<0.001	1 (0–4)	1 (0–3)	0.28
Presenting symptoms, %							
Sore throat	12	13	9	<0.001	17	8	0.04
Cough	53	58	38	<0.001	56	36	0.009
Shortness of breath	36	44	11	<0.001	22	10	0.005
Fever	62	68	44	<0.001	50	43	0.007
Headache	11	13	8	<0.001	14	8	0.006
Nausea or vomiting	12	13	7	<0.001	6	7	0.004
Diarrhoea	16	18	11	<0.001	14	10	0.008
Myalgia or arthralgia	21	23	16	<0.001	26	15	0.003
Vital signs, mean ± SD							
Temperature (°C)	37.5 ± 1.1	37.6 ± 1.1	37.2 ± 1.0	<0.001	37.3 ± 1.2	37.2 ± 1.0	0.55
Respiration rate (per min)	20 ± 6	20 ± 6	17 ± 4	<0.001	17 ± 4	17 ± 3	0.85
O_2 saturation room air (%)	94 ± 6	93 ± 6	97 ± 3	<0.001	97 ± 3	97 ± 3	0.60
SBP (mm Hg)	135 ± 25	135 ± 25	137 ± 24	0.14	129 ± 22	139 ± 25	0.04
DBP (mm Hg)	75 ± 15	76 ± 15	73 ± 15	0.05	69 ± 15	74 ± 15	0.07
Pulse rate (bpm)	84 ± 16	85 ± 16	77 ± 13	<0.001	73 ± 11	77 ± 14	0.13
Laboratory test results							
Creatinine increase (>25%)[b]	30	33	8	<0.001	25	12	0.007
Lymphocytes (×1000/μL), median (IQR)	0.9 (0.6–1.3)	0.9 (0.5–1.3)	0.9 (0.6–1.2)	0.87	0.7 (0.5–1.1)	0.9 (0.6–1.2)	0.41
CRP (mg/L), median (IQR)	31 (8–84)	38 (10–95)	13 (3–43)	<0.001	26 (6–58)	12 (2–36)	0.02

Groups were compared using Student's *t*, Wilcoxon or chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. O_2, oxygen; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute; mTOR, mechanistic target of rapamycin.
[a]In dialysis patients only.
[b]In transplant recipients only.

heart rate and less often had an abnormality on chest X-ray or CT scan (Table 3).

28-day mortality

A total of 314 of 1068 patients (29%) died among those who were admitted to the hospital at first presentation. Nine of 36 patients (25%) who were not hospitalized at first presentation died after they returned for admission, whereas 19 of 319 patients (6%) died who were not hospitalized initially but also did not return for a second assessment. The mortality rate in those who were hospitalized at the second presentation did not differ from that of patients who were admitted at the first presentation ($P = 0.61$). However, the mortality rate was signficantly lower among patients who were not hospitalized at the first visit and did not return for reassessment ($P < 0.001$) (Figure 2). Mortality also did not differ between those who were hospitalized at the first presentation and those who returned for a second presentation (29% versus 25%; $P = 0.60$). Among those who had delayed hospital admission, all nine deaths occurred in HD patients. KRT modality did not appear as a strong predictor in the multivariate model.

Predictors of prognosis in those not admitted at first presentation

Older age, prior tobacco use, higher clinical frailty score, autoimmune disease and shortness of breath were identified as predictors of 28-day mortality in patients who were not hospitalized after their initial presentation with COVID-19 (Table 4). Older age, prior tobacco use and increased shortness of breath were identified as predictors of deferred hospital attendance (Supplementary data, Table S3) and hospital admission at the second assessment (Supplementary data, Table S4).

Table 2. Patient characteristics at first and second presentation in those who presented on two separate occasions ($N = 36$)

Characteristics	Patient characteristics by presentation		
	First presentation ($n = 36$)	Second presentation ($n = 36$)	P-value
Patient identification, *n*			0.03
Symptoms only	85	93	
Symptoms and contact	15	4	
No symptoms but contact	0	0	
Routine screening	0	4	
Presenting symptoms, %			
Sore throat	17	1	0.41
Cough	56	64	0.18
Shortness of breath	22	53	0.002
Fever	50	64	0.13
Headache	14	19	0.16
Nausea or vomiting	6	19	0.03
Diarrhoea	14	25	0.16
Myalgia or arthralgia	26	25	0.71
Vital signs, mean ± SD			
Temperature (°C)	37.3 ± 1.2	37.6 ± 0.9	0.19
Respiration rate (per min)	17 ± 4	23 ± 9	0.003
O_2 saturation room air (%)	97 ± 3	90 ± 10	0.001
SBP (mm Hg)	129 ± 22	133 ± 26	0.44
DBP (mm Hg)	69 ± 15	70 ± 14	0.67
Pulse rate (bpm)	73 ± 11	78 ± 13	0.04
Laboratory test results			
Creatinine increase (>25%)[a]	25	62	0.001
Lymphocytes (×1000/μL), median (IQR)	0.7 (0.5–1.1)	0.7 (0.4–0.9)	0.02
CRP (mg/L), median (IQR)	26 (6–58)	73 (21–151)	<0.001

Groups were compared using Student's *t*, Wilcoxon or chi-square test as appropriate. O_2, oxygen; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute.
[a]In transplant recipients only.

DISCUSSION

In this study from the ERACODA, we found that 25% of patients on KRT who presented with a COVID-19 diagnosis did not require hospitalization, due to milder clinical symptoms. Only 10% of these patients returned to the hospital with progressive illness and required hospitalization after a second clinical assessment. For most of these patients, the return to the hospital was necessary within 1 week from their initial attendance. Reassuringly, the 28-day survival of those who had a deferred hospital admission did not differ from those who were admitted at their initial clinical presentation. Our data indicate that stratification for admitting KRT patients presenting with COVID-19 can be done safely based on clinical parameters.

These findings will affect our approach to management of these patients. Hospital bed occupancy due to patients with COVID-19 may increase during the second and third waves of the pandemic while awaiting the full effects of vaccination programmes. It may be necessary to clinically triage patients presenting with a COVID-19 diagnosis. This study suggests that, despite being an extremely vulnerable group, a clinical risk stratification strategy to determine the optimal location of care for patients receiving KRT presenting with COVID-19 can be justified. Those with mild symptoms or minor derangements of diagnostic tests may be managed as outpatients at home or in dedicated dialysis facilities or clinics. However, it is essential to ensure this is supported by follow-up with teams dedicated to deliver this remotely or face-to-face, during their dialysis visits or close follow-up at the outpatient wards for kidney transplant recipients. Our study identified that older age, frailty, a prior history of smoking and self-reported shortness of breath are associated with hospital re-attendance in patients not hospitalized after the initial presentation. Older age and frailty were previously recognized as predictors of hospitalization of HD patients with COVID-19 infection [9]. The possibility of predisposition to COVID-19 pneumonia in the context of underlying smoking-induced lung damage is high. Bacterial co-infection in the general population is believed to be less frequent (3.5%), but in hospitalized patients, the risk of secondary bacterial infection is significant at 14.3% and many patients receive antibiotics, with worsening respiratory illness [10]. These reports justify closer outpatient monitoring of risk factors invulnerable KRT patients.

Outpatient management of the general population with COVID-19, after presenting in Emergency Departments (EDs), has been primarily examined in patients who are typically young and not multimorbid, unlike the dialysis cohort [11]. In these low-risk patients, a minority require hospitalization after being discharged home from the ED. ED revisits occurred for 13.7% of patients, which is similar to our study. The inpatient admission rate at 30 days was 4.6%, with 0.7% requiring intensive care [11]. The importance of early and optimum outpatient care of COVID-19 patients is now recognized, based on the current understanding of the biophysical distribution of COVID-19 viral particles. It is well-recognized that COVID-19 exists in the exhaled air of an infected person, raising the risk of re-inoculation. In hospitalized patients, negative-pressure rooms are used to reduce the spread of communicable diseases outside

Table 3. Characteristics of patients admitted to hospital after the first and second presentation

Characteristics	Admitted after first presentation ($n = 1068$)	Admitted after second presentation ($n = 34$)	P-value
Sex (male), %	62	62	0.97
Age (years), mean ± SD	64 ± 14	71 ± 14	0.005
BMI (kg/m^2), mean ± SD	27 ± 5	27 ± 5	0.83
Race, %			0.49
Asian	3	6	
Black or African descent	5	9	
White or Caucasian	86	82	
Other or unknown	6	3	
Tobacco use, %			0.03
Current	7	0	
Prior	22	41	
Never	47	44	
Unknown	24	15	
CFS (AU), mean ± SD	3.7 ± 1.8	4.0 ± 1.7	0.34
Patient identification, *n*			0.37
Symptoms only	75	88	
Symptoms and contact	15	12	
No symptoms but contact	5	0	
Routine screening	5	0	
COVID-19 test result, *n*			0.77
Positive	92	91	
Negative	5	6	
Intermediate/unknown	2	3	
Abnormality on X-ray (yes), *n*	44	15	0.002
Abnormality on CT scan (yes), *n*	41	6	<0.001
Comorbidities, %			
Obesity	23	16	0.33
Hypertension	83	82	0.92
Diabetes mellitus	40	47	0.41
Coronary artery disease	30	35	0.49
Heart failure	21	18	0.65
Chronic lung disease	12	18	0.37
Active malignancy	7	9	0.69
Autoimmune disease	5	9	0.31
Primary kidney disease, %			
Primary glomerulonephritis	16	15	0.84
Pyelonephritis	3	0	0.34
Interstitial nephritis	5	3	0.66
Hereditary kidney disease	10	9	0.92
Congenital diseases	2	0	0.43
Vascular diseases	12	18	0.32
Secondary glomerular disease	7	9	0.59
Diabetic kidney disease	22	33	0.12
Other	13	6	0.25
Unknown	11	6	0.37
Dialysis (yes), %	67	79	0.13
HD[a]	99	100	0.73
PD[a]	1	0	
Residual diuresis ≥200 mL/day[a]	33	48	0.08
Transplant waiting list status[a], %			0.39
Active on waiting list	11	7	
In preparation	10	7	
Temporarily not on list	10	4	
Not transplantable	64	81	
Unknown	5	0	
Kidney transplant (yes), %	34	21	
Time since transplantation[b], %			0.57
<1 year	8	14	
1–5 years	31	43	
>5 years	61	43	
Medication, %			
ACE inhibitor use (yes)	17	21	0.37
ARB inhibitor use (yes)	15	24	0.18

Continued

Table 3. Continued

Characteristics	Admitted after first presentation ($n = 1068$)	Admitted after second presentation ($n = 34$)	P-value
Immunosuppressant use, %			
Prednisone	86	91	0.63
Tacrolimus	67	64	0.79
Cyclosporine	11	0	0.49
Mycophenolate	58	45	0.39
Azathioprine	4	0	0.75
mTOR inhibitor	12	18	0.81
Disease characteristics			
Days from symptom onset, median (IQR)	2 (0–5)	1 (0–4)	0.32
Presenting symptoms, %			
Sore throat	13	18	0.63
Cough	58	56	0.93
Shortness of breath	44	24	0.05
Fever	68	50	0.02
Headache	13	15	0.67
Nausea or vomiting	13	6	0.21
Diarrhoea	18	15	0.37
Myalgia or arthralgia	23	27	0.28
Vital signs, mean ± SD			
Temperature (°C)	37.6 ± 1.1	37.4 ± 1.2	0.21
Respiration rate (per min)	20 ± 6	17 ± 4	0.006
O_2 saturation room air (%)	93 ± 6	96 ± 3	0.003
SBP (mm Hg)	135 ± 25	129 ± 22	0.19
DBP (mm Hg)	76 ± 15	69 ± 15	0.009
Pulse rate (bpm)	85 ± 16	74 ± 11	<0.001
Laboratory test results			
Creatinine increase (>25%)[b]	33	25	0.52
Lymphocytes (×1000/μL), median (IQR)	0.9 (0.5–1.3)	0.7 (0.5–1.1)	0.42
CRP (mg/L), median (IQR)	38 (10–95)	29 (5–63)	0.14

Groups were compared using Student's *t*, Wilcoxon or chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. DBP, diastolic blood pressure; O_2, oxygen; SBP, systolic blood pressure; mTOR, mechanistic target of rapamycin.
[a]In dialysis patients only.
[b]In transplant recipients only.

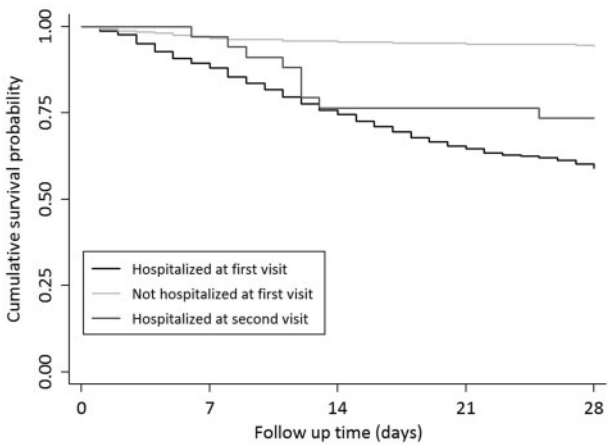

FIGURE 2: Kaplan–Meier survival curves for 28-day mortality (from date of first presentation)*. (1) Hospitalized at first visit = hospitalized at first visit excluding those who were admitted also on second visit ($n = 1089$, events = 314). (2) Not hospitalized at first visit = not admitted on first visit and did not return for second visit ($n = 319$, events = 19). (3) Hospitalized at second visit = not admitted on first visit but returned for a second visit and hospitalized ($n = 34$, events = 9). *P value = 0.61 for cumulative survival difference between 1 and 3 and $P < 0.001$ for survival difference between 1 and 2 and 2 and 3.

of the room. In patients treated outside the hospital, this could be achieved by spending time outdoors or indoors with windows open. Oxygen, anti-thrombotic therapy and new or repurposed immunomodulatory and antiviral drugs are also in development or in trials to help facilitate outpatient management to the extent possible.

At first presentation with COVID-19, the proportion of transplant patients admitted was higher than that at the second presentation (33% versus 21%), possibly deemed at higer risk or suggesting a potential lag in the evolution of symptoms in the HD cohort. This may also be due to potentially earlier identification of HD patients compared with transplant patients, as a larger proportion of cases on HD were identified through routine screening. Alternatively, this could also imply a lower threshold for admission of home-based transplant patients in contrast to HD patients who routinely attend for in-centre dialysis. In a publication from Spain that reported on the course of a small cohort of HD patients, a mild clinical presentation at diagnosis did not necessarily guarantee a benign course, as all patients ultimately developed radiological abnormalities—hence the need for a robust pathway of monitoring if discharged at the outset [12]. The safety of outpatient management of HD recipients was reported in another study by Medjeral-

Table 4. Predictors of 28-day mortality in those not admitted to hospital at first presentation ($n = 355$, events = 28) (presented as hazard ratios with 95% confidence intervals)

Characteristics	Univariable	P-value	Multivariable	P-value
Age (years)	1.06 (1.03–1.10)	<0.001	1.05 (0.99–1.10)	0.08
Sex (male)	1.43 (0.66–3.09)	0.37		
Race				
White/Caucasian	Ref.			
Asian	3.04 (0.91–10.17)	0.07		
Black/African descent	1.10 (0.26–4.69)	0.90		
Other/unknown	1.32 (0.18–9.83)	0.78		
Tobacco use				
Never	Ref.			
Current	0.98 (0.13–7.64)	0.98		
Prior	2.58 (1.12–5.98)	0.027	2.51 (1.01–6.25)	0.05
Unknown	0.52 (0.18–1.53)	0.24		
CFS (AU)	1.64 (1.31–2.07)	<0.001	1.41 (1.05–1.89)	0.02
X-ray abnormality (yes)	4.08 (0.37–45.04)	0.25		
CT scan abnormality (yes)	–	–		
BMI (kg/m^2)	1.04 (0.98–1.10)	0.17		
Diabetes (yes)	1.62 (0.77–3.41)	0.20		
Hypertension (yes)	0.70 (0.28–1.73)	0.44		
Lung disease (yes)	1.74 (0.66–4.59)	0.26		
Active malignancy	2.50 (0.59–10.53)	0.21		
Autoimmune disease	4.73 (1.64–13.65)	0.004	3.85 (0.74–19.97)	0.11
ARB use (yes)	1.75 (0.77–3.98)	0.18		
ACEi use (yes)	1.02 (0.35–2.94)	0.97		
Dialysis (versus transplant)	4.91 (0.67–36.15)	0.118		
Days between two presentations	1.03 (0.97–1.09)	0.32		
Disease characteristics				
COVID-19-related symptoms				
Cough (yes)	1.58 (0.70–3.55)	0.27		
Fever (yes)	1.24 (0.58–2.68)	0.58		
Shortness of breath (yes)	3.26 (1.39–7.62)	0.006	3.23 (1.31–7.96)	0.01
Headache (yes)	1.83 (0.62–5.40)	0.26		
Diarrhoea (yes)	1.25 (0.43–3.65)	0.68		
Nausea/vomiting (yes)	–			
Vital signs				
Temperature (°C)	1.16 (0.77–1.74)	0.48		
Respiration rate (per min)	1.07 (0.96–1.19)	0.24		
O_2 saturation (%)	0.87 (0.78–0.98)	0.017		
Pulse rate (bpm)	1.00 (0.96–1.03)	0.84		
Laboratory test results				
Lymphocyte (×1000/μL)	1.00 (0.76–1.31)	0.99		
CRP (mg/L)	1.00 (0.99–1.01)	0.36		

bpm, beats per minute; O_2, oxygen.

Thomas *et al.* [9]. The authors found progressively decreasing blood oxygen saturations over the first three dialysis sessions in the cohorts that progressed to future hospital admission or death [9]. This finding is replicated in our study, where hypoxia was evident at the second presentation of patients who had satisfactory vital parameters a few days earlier.

In the transplantation cohort, there have been reports of successful management of patients as outpatients through a systematic strategy to triage outpatient and inpatient care. In one study, symptom resolution was achieved without the need for hospitalization through early management of bacterial infections and minor adjustment of immunosuppression [13, 14].

The 28-day mortality of KRT recipients has been reported in the published literature to vary from 15% to 29% [13–15]. This corresponds with the 28-day mortality for patients hospitalized at the first (29%) and the second presentation (25%) in our study. Patients who did not return for a second presentation had a 28-day mortality of 6%. The causes of death in the latter instances are not known. In a large study from a major healthcare system in the USA, the mortality of patients with COVID-19 was predicted by a three-variable prediction model. These were older age, low oxygen saturation during the encounter and the type of encounter (inpatient versus outpatient versus telehealth). In this dataset, patients who were alive were more likely to have had their initial encounter at a hospital rather than at an outpatient or telehealth setting compared with patients who died (odds ratio 15.59; $P < 0.0001$) [16]. This reinforces the need for close follow-up of patients if they are deemed to be safe for discharge at their first consultation, especially if they have risk factors and comorbidities.

The key strength of our study is that it was performed in real-life conditions during the first wave of the pandemic, with access to complete sociodemographic and clinical datasets from multiple centres, including admissions data such as laboratory reports, diagnostic imaging and COVID-19 treatment data. Consequently this has allowed us to analyse the risk of hospital admission related to COVID-19 adjusted for confounders, thus minimizing possible bias. Our data highlight that supported outpatient care of patients on KRT is a viable management proposition for healthcare institutions. Although the reported prognosis predictors are not modifiable, knowing them can help us prioritize initial and follow-up care for these 'at-risk' patient groups.

Our study has its limitations. The lack of availability of widespread antigen or antibody testing during the first wave of the pandemic and the extent of disease transmission being unclear could have led to reporting bias, as some patients may have had mild symptoms and did not present to the hospital for evaluation. This is especially true for transplant recipients. More detailed virology data with strain types and viral load may have added strength to the prognostication criteria but were unavailable at the time. The study did not collect any centre-specific protocols for referrals, admissions or discharges. However, the median time between the first and second visit was 5 days (IQR 2–7), with worsening of disease symptoms in those who returned for a second visit (Table 2). Therefore it seems unlikely that centres would have adopted protocols to discharge or arrange revisits to hospitals on an elective basis during the pandemic. Second presentations were determined mainly by disease symptoms and severity.

Balancing safe patient care with available resources remains a priority as we encounter current and subsequent waves of the pandemic. This study provides some insights for clinicians to develop and adopt strategies for patient pathways when caring for outpatient kidney transplant and dialysis recipients. As with other illnesses, individual patient circumstances and clinical judgement must be factored into the decision to admit or not to admit to the hospital at any given point in time.

DATA AVAILABILITY STATEMENT

Collaborators that entered data in ERACODA remain the owners of these data. The database information can therefore not be disclosed to any third party without the prior written consent of all data providers, but the database will be made available to the editorial offices of medical journals when requested. Research proposals can be submitted to the Working Group via COVID.19.KRT@umcg.nl. If deemed of interest and methodologically sound by the Working Group and Advisory Board, the analyses needed for the proposal will be carried out by the Management Team.

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AUTHORS' CONTRIBUTIONS

All authors contributed to data collection, study design, data analysis, interpretation and drafting of this article.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to declare.

APPENDIX 1

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