

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

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COVID-19 – second presentation

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ABSTRACT

Rationale & Objective. Patients on kidney replacement therapy (KRT) are at a very high risk of COVID-19. Triage pathway for KRT patients presenting with varying severity of COVID-19 illness remains ill-defined. We studied clinical characteristics of patients at initial and subsequent hospital presentations and its impact on patient outcomes.

Study Design, Setting, Participants. 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 during first presentation and those representing after non-admission at initial triage. Predictors of outcomes (Hospitalisation, 28-day mortality) were determined for those not hospitalized at first presentation.

Results. Amongst 1423 KRT patients with COVID-19 (Hemodialysis=1017/Transplant=406), 25% (n=355) were not hospitalized at first presentation (30% Hemodialysis/13% Transplant). Of these non-hospitalized patients, 10% (n=36) re-presented second time, with a 5-day median interval between two presentations (Interquartile interval 2-7 days). Patients who re-presented had worsening respiratory symptoms, a fall in oxygen saturation (97% vs. 90%) and rise in C-reactive protein between attendances (26 vs. 73 mg/L). Patients on second presentation were older (72 vs. 63 years), had early respiratory symptoms and lung imaging abnormalities compared with those who did not return second time. The 28-day mortality for those admitted at first or second presentations was not significantly different (25% vs. 29%, p=0.6). Higher age, prior smoking history, higher clinical frailty score and self-reported

shortness of breath at first presentation, were identified as predictors of mortality in those discharged at initial triage.

Conclusions. The study provides evidence that KRT patients with COVID-19 and mild pulmonary abnormalities with lack of pulmonary insufficiency can be safely discharged, 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 optimise resource utilisation during the ongoing pandemic.

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

KEY LEARNING POINTS

What is already known about this subject?

Clinical triage pathway for kidney replacement therapy patients presenting with COVID-19 illness of varying severity has not been well defined. In the current phase of the pandemic, kidney patients are at high risk but presenting with varying degrees of severity. Ongoing pandemic has seen a major strain in hospital resources and clinical pathways affecting overall care. ERACODA is a comprehensive Pan European Multicentre Registry with prospective data collection on COVID.

What this study adds?

This study focusses specifically on patients who were not admitted on initial presentation but represented to hospitals second time and compares clinical characteristics and

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5 outcomes of hospitalisation and 28 day mortality with other cohorts. Such multicentre
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7 large dataset on this topic has not been presented to our knowledge.

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9 The study informs the outcomes predictors on those admitted on second presentation and
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11 their clinical characteristics indicating how to clinically risk stratify kidney patients
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13 safely on initial triage. This provides evidence, reassurance for clinicians and clinical
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15 practice parameters on the basis of which such patients with varying COVID severity can
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17 be managed when presenting to hospitals.
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21 **What impact this may have on practice or policy?**

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23 The study will help allow optimal resource utilisation for COVID and also create
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25 capacity for treating non COVID related illness in kidney patients. This is a great
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27 learning from COVID19 Wave 1 and such knowledge transfer will support the restoration
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29 plan for renal services.
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1 INTRODUCTION

2 The COVID-19 pandemic has caused devastation to human lives and major disruption of
3 health care systems and individual patient care around the world. Patients with advanced
4 chronic kidney disease (CKD) on kidney replacement therapy (KRT) with dialysis or
5 transplantation, have been identified as specifically vulnerable groups (1). If infected
6 with SARS-CoV-2, these patients often require high intensity care and major utilization
7 of hospital resources. During the ongoing pandemic, the optimal care pathway and
8 triaging for KRT patients presenting with varying severity of COVID-19 is unknown.

9 Whilst 80% of patients with COVID-19 have mild symptoms, approximately 10–20% of
10 patients can develop severe disease (2). Understanding of the factors associated with
11 progression of symptoms from the asymptomatic- stage through to severe illness is
12 essential for developing efficient and appropriate triage systems. Avoidance of
13 unnecessary hospitalizations, when clinically appropriate and safe, will offer protection
14 of COVID-19 patients from potential exposure to hospital acquired infections, minimize
15 the risk of transmitting COVID-19 infections to others who don't have the illness, allow
16 continuation of standard and routine care, cause less disruption to patient lives, and avoid
17 overwhelming the healthcare system. There is limited information on risk factors that
18 precipitate need for hospital admission, worsening of symptoms following discharge, and
19 readmission outcomes in KRT patients with COVID-19. Characteristics and outcomes of
20 patients with mild to moderate disease who are not hospitalized have been scarcely
21 reported in the literature (3). As the pandemic is sustained through second and possible
22 future waves, with a simultaneous increase in identification rates from enhanced testing,
23 and continued disruption of routine care, we urgently need to establish optimum triage

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5 24 tools to support decision-making on hospitalization of patients on KRT affected by
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7 25 COVID-19.
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10 26 We analyzed the data of patients receiving kidney replacement therapy who
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12 27 presented with COVID-19. Clinical features, laboratory results, and outcome of
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14 28 hospitalized and non-hospitalized patients at first presentation were studied and compared
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17 29 with characteristics of patients who returned for a second assessment. In addition, we
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19 30 identified predictors of subsequent admission and poor outcomes in those not admitted at
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21 31 their initial presentation.
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33 **MATERIALS AND METHODS**

34 *Study design and participants*

35 This observational study used data from the ERACODA database, which was established
36 in March 2020 (4). This initiative is endorsed by the European Renal Association –
37 European Dialysis and Transplantation Association (ERA-EDTA) and currently involves
38 the cooperation of more than 200 physicians representing 130 centers in 31 countries,
39 mostly in Europe and bordering the Mediterranean Sea. Data were collected on adult
40 (≥ 18 years old) patients with kidney failure, treated with either long-term dialysis or a
41 functioning kidney allograft. Patients were diagnosed with COVID-19 illness, based on a
42 positive result on a real-time reverse polymerase chain reaction assay of nasal or
43 pharyngeal swab specimens, and/or compatible findings on computer tomography scan of
44 the lungs. Data were gathered from outpatients as well as hospitalized patients.
45 Physicians responsible for the care of these patients registered detailed demographic and
46 clinical data including information pertaining to disease severity, treatment and
47 outcomes.

48 The ERACODA database is hosted at the University Medical Center Groningen,
49 the Netherlands. Data are recorded using REDCap software (Research Electronic Data
50 Capture, Vanderbilt University Medical Center, Nashville, TN, USA) (4). Patient
51 identifiable information was stripped from each record and data were stored,
52 pseudonymized. The study was approved by the Institutional Review Board of the
53 University Medical Center Groningen (the Netherlands), who deemed the collection and
54 analysis of data exempt from ethics review regarding the Medical Research Involving
55 Human Subjects Act (WMO).

56 ***Data collection***

57 For the current study, all patients with COVID-19 diagnosis between February 1st
58 and June 30th, 2020 with complete clinical datasets on hospitalizations and day 28
59 outcomes, were included in the analysis.

60 Detailed information was collected on patient characteristics (including age, sex,
61 race, frailty score, comorbidities, hospitalization and medication use), and COVID-19
62 related characteristics (reason for COVID-19 screening, presenting symptoms, vital signs
63 and laboratory test results) at presentation. Frailty was assessed on a scale of 1 to 9 based
64 on the Clinical Frailty Scale (CFS) (5). The CFS uses clinical descriptors and pictographs
65 to generate a frailty score for a patient, a score of 1 represents very fit and score of 9
66 represents terminally ill patient. Comorbidities were recorded from patient records and
67 obesity was defined as a Body Mass Index (BMI) ≥ 30 kg/m². Information was also
68 collected on practical and logistic considerations which mainly referred to organizational
69 and local infrastructural constraints. We kept the definition broad to tease out the
70 proportion of patients where decision making for clinical triage was based on patient and
71 disease characteristics alone.

72 ***Statistical analysis***

73 First, we examined characteristics of hospitalized and non-hospitalized patients at their
74 first and second presentations. Second, we assessed characteristics of patients who were
75 not admitted to the hospital initially but presented a few days later. To assess the disease
76 course, we compared characteristics of the first and second presentations of those patients
77 who presented twice. Continuous data are presented as mean \pm standard deviation (SD)
78 or as median with interquartile range in case of a non-normal distribution. Categorical

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5 79 data are presented as percentages. Characteristics were compared between groups using
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7 80 the student's t-test in case of continuous variables (Mann-Whitney U-test in case of non-
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9 81 normally distributed data) and Pearson chi-2 statistics in case of categorical variables.

11 82 To examine 28-day mortality, cumulative survival probabilities were plotted in
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14 83 Kaplan-Meier curves and compared using Log rank-tests for three groups of patients: 1)
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16 84 those hospitalized at first visit; 2) those not hospitalized at first visit who did not return
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18 85 for a second visit and 3) those not hospitalized at first visit who returned for a second
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21 86 presentation.

23 87 For those patients who were discharged after the first presentation, we identified
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25 88 predictors of 28-day mortality, hospitalization and second presentation using a backward
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28 89 elimination procedure. For 28-day mortality this was done using Cox proportional-
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30 90 hazards regression, whereas predictors for hospitalization and second presentation were
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32 91 identified using a Fine and Gray competing risk model to account for the competing risk
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34 92 of mortality (7). Candidate predictors were selected in a two-stage process. First,
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37 93 candidate factors were selected based on clinical knowledge. These factors include age,
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39 94 sex, race/ethnicity, tobacco use, frailty score, X-ray finding, CT scan finding, obesity,
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41 95 diabetes, hypertension, lung disease, active malignancy, auto-immune disease,
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44 96 ACEi/ARB use, type of kidney replacement therapy (dialysis/transplant), COVID-19
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46 97 related symptoms and vital signs including cough, fever, shortness of breath, headache,
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48 98 diarrhea, nausea/vomiting, temperature, oxygen saturation, respiration rate, pulse rate,
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51 99 lymphocyte count and C-reactive protein. Subsequently, each of these variables was
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53 100 examined in a univariable analysis and those with a p-value <0.1 were considered
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55 101 candidate predictors for the multivariable model. Those variables with a p-value <0.2 in
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102 the multivariable model, were identified as predictors and were included in the final
103 model (6).

104 All analyses were performed using Stata version 14.0 (College Station, TX). A 2-
105 sided P value less than 0.05 indicated statistical significance.

RESULTS

A total of 1,596 patients on KRT presented for evaluation of COVID-19 symptoms between February 1st and June 30th, 2020. After excluding patients with missing information on hospitalization (n=27), 28-day clinical status (n=121) or both (n=25), 1,423 patients were included for analysis. Of these patients, at first presentation 1,068 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 1,017 (71%) were dialysis patients, (99% hemodialysis and 1% peritoneal dialysis). From this cohort of 1,423 patients, 355 patients (25%) were not admitted at first presentation (13% (n=53) of kidney transplant patients/ 30% (n=302) of dialysis patients). The gender distribution, age and frailty score of these 355 non-hospitalized patients were similar as in patients who were hospitalized after their initial assessment. However, the non-hospitalized patients had lower CRP values (13 mg/L versus 38 mg/L) and less frequent pulmonary symptoms including cough (38% versus 58%) and shortness of breath (11% versus 44%), 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 attendance. Median duration of in-patient stays among those hospitalized was 15

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5 130 days (interquartile range: 9-23 days). Only 5 patients were discharged alive within 24
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7 131 hours of hospital admission.

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10 132 ***Second presentation***

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12 133 Thirty-six of the 355 patients (10%) who were not hospitalized at their first assessment,
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14 134 presented themselves for a second time with clinical illness (Table 1). Of these 36
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16 135 patients, the numbers of transplant and dialysis recipients were 22% (8) and 78% (28),
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18 136 respectively. Amongst the 355 patients who were not hospitalized initially, practical and
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20 137 logistical considerations precluded hospital admission the first time round for 9% of
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22 138 patients who returned for a second assessment compared to 1% of those who did not
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24 139 return. (Table S1). Figure S1 shows the distribution of patients with a second presentation
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26 140 according to their country of residence. Second attendance cases formed $\leq 5\%$ of the
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28 141 reported cases in each country, except for France where 24% of the reported cases
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30 142 returned for a second assessment (Table S2). The median time interval between the first
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32 143 and second presentation was 5 days (interquartile range: 2 to 7 days) (Figure S2). Patients
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34 144 who presented a second time, were older, more often had a history of prior tobacco use
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36 145 and more frequently had diabetic kidney disease compared with those who did not re-
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38 146 present at the hospital (Table 1). Furthermore, these patients more often had pulmonary
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40 147 symptoms including cough (56% versus 36%), shortness of breath (22% versus 10%),
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42 148 abnormalities on chest X-ray (14% versus 8%), lower mean systolic blood pressure (129
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44 149 ± 26 mmHg versus 139 ± 25 mmHg) and a higher median CRP value 26 mg/L
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46 150 [interquartile interval (6, 58)] versus 12 mg/L [interquartile interval (2, 36)] on initial
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48 151 attendance compared to those patients who did not return for a second presentation. In
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5 152 those identified on first presentation through screening (routine or because of contact),
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7 153 did not return for a second presentation.
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10 154 ***Evolution of symptoms, vital signs and laboratory results from first hospital attendance***
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12 155 ***to the second presentation***
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15 156 Patients who sought healthcare input for a second time had clinical symptoms
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17 157 characterized by worsening of respiratory illness, with symptoms of cough, shortness of
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19 158 breath, and a decline in their vital parameters, namely an increase in respiration rate, a
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21 159 decrease in blood oxygen saturation (from 97% to 90%) and an increase in pulse rate
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23 160 (from 73 beats/minute to 78 beats/minute). Temperature and blood pressure did not
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25 161 change significantly between first and second presentations (Table 2). An increase in
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27 162 CRP (from 26 mg/L to 73 mg/L) was also noted at their deferred presentation.
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31 163 ***Comparison of characteristics of patients hospitalized at their first presentation and at***
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33 164 ***baseline, of those patients who returned for a second hospital episode.***
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36 165 Compared to patients admitted after their initial consultation, those who were admitted
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38 166 later, were older, more often had prior tobacco use, less often had shortness of breath and
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40 167 fever, had a lower respiratory rate, a higher oxygen saturation, a lower diastolic blood
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42 168 pressure and heart rate and less often had an abnormality on chest x-ray or CT scan at the
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44 169 time of their initial assessment (Table 3).
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48 170 ***28-day mortality***
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50 171 A total of 314 of 1068 patients (29%) died among those who were admitted to the
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52 172 hospital at first presentation. Nine of 36 patients (25%), who were not hospitalized at first
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54 173 presentation, died after they returned for re-admission, whereas 19 of 319 patients (6%)
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56 174 died who were not hospitalized initially but also did not return for a second assessment.
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5 175 Mortality rate in those who were hospitalized at the deferred admission did not differ
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7 176 from that of the rate in patients who were admitted at their first presentation (p=0.61).
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9 177 However, mortality rate was higher amongst patients who were not hospitalized at first
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11 178 visit and did not return for re-assessment (p<0.001) (Figure 2). Mortality also did not
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13 179 differ between those who were hospitalized at first presentation and those who returned
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15 180 second presentation (29% vs. 25%, p=0.60). Amongst those who had delayed hospital
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17 181 admission, all 9 deaths occurred in hemodialysis patients. RRT modality as dialysis or
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19 182 transplant did not appear as a strong predictor in the multivariate model.
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24 183 ***Predictors of prognosis in those not admitted at first presentation.***

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26 184 Higher age, prior tobacco use, higher clinical frailty score, auto-immune disease and
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28 185 shortness of breath were identified as predictors of 28-day mortality in patients who were
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30 186 not hospitalized after their initial presentation with COVID-19 (Table 4). Higher age,
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32 187 prior tobacco use, and increase of shortness of breath were identified as predictors of
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34 188 deferred hospital attendance (Table S3) and hospital admission at their second
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36 189 assessment. (Table S4).
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DISCUSSION

In this study from the ERACODA Database, we found that 25% of patients on KRT, who presented with COVID-19 diagnosis, were not hospitalized, 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 hospital was necessary within one week after 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 consult. Our data indicate that stratification for admitting KRT patients presenting with COVID-19 can be done safely based on clinical parameters.

These findings will have repercussions on our approach to management of these patients. Hospital bed occupancy due to patients with COVID-19 may rise during the second and third waves of the pandemic whilst awaiting the effects of vaccination programs. It is therefore necessary to triage patients presenting with 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 kidney replacement therapy presenting with COVID-19 can be justified. Those with mild symptoms or minor derangements of diagnostic tests may be managed as out-patients at home or in dedicated dialysis facilities or clinics. However, it is essential to ensure follow-up of these patients with teams dedicated to deliver this remotely and face-to-face, during their dialysis visits or close follow-up at the outpatient ward for kidney transplant recipients. Our study has identified that older age, frailty, a prior history of smoking and self-reported shortness of breath are associated with a hospital re-attendance

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5 214 in patients not hospitalized after initial presentation. Older age and frailty were
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7 215 previously recognized as predictors of hospitalization of hemodialysis patients with
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9 216 COVID-19 infection (9). The possibility of predisposition to COVID-19 pneumonia in
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11 217 the context of underlying smoking-induced lung damage is high. Bacterial co-infection in
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13 218 the general population is believed to be less frequent (3.5%), but in hospitalized patients,
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15 219 the risk of secondary bacterial infection is significant at 14.3% and many patients receive
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17 220 antibiotics, with worsening respiratory illness (10). These reports justify closer out-
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19 221 patient monitoring of the vulnerable KRT patients.
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23 222 Safety of the out-patient management of the general population with COVID-19
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25 223 illness, after presenting in Emergency Departments (ED), have been primarily examined
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27 224 in patients who are typically young and not multi-morbid as is the dialysis cohort(11). In
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29 225 these low-risk patients, a minority would require hospitalization after being discharged
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31 226 home from the ED. The ED revisits occurred for 13.7% of patients which is almost
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33 227 similar as in our study. The inpatient admission rate at 30 days was 4.6%, with 0.7%
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35 228 requiring intensive care (11). Increasingly, the importance of early out-patient care of
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37 229 COVID-19 patients is gathering pace, based on the current understanding of the
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39 230 biophysical distribution of COVID-19 viral particles. It is well-recognized that COVID-
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41 231 19 exists in the exhaled air of an infected person raising the risk of re-inoculation. In
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43 232 hospitalized patients, negative pressure rooms are used largely to reduce spread of
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45 233 communicable diseases outside of the room. In patients treated outside the hospital this
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47 234 could be achieved by spending time outdoors or indoors with windows open. Oxygen,
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49 235 anti-thrombotic therapy and new or re-purposed immunomodulatory and anti-viral drugs
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5 236 are in development or in trials to help facilitate out-patient management to the extent
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7 237 possible.

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9 238 At first presentation with COVID-19, the proportion of transplant patients
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11 239 admitted was higher than that at the second presentation (33% vs 21%), suggesting a
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13 240 potential lag before the evolution of symptoms in the hemodialysis cohort. This may be
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15 241 due to potentially earlier identification of hemodialysis patients compared to transplant
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17 242 patients as a larger proportion of cases in hemodialysis were identified through routing
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19 243 screening. Alternatively, this could also imply a lower threshold for admission for home-
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21 244 based transplant patients in contrast to HD patients who attend for in-centre dialysis
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23 245 routinely. In a publication from Spain, which reported on the course of a small cohort of
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25 246 hemodialysis patients, a mild clinical presentation at diagnosis did not necessarily
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27 247 guarantee a benign course, as all patients ultimately developed radiological abnormalities
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29 248 – hence the need for a robust pathway of monitoring if discharged at the outset (12). The
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31 249 safety of outpatient management of hemodialysis recipients has been reported in another
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33 250 study by Medjeral-Thomas et al. The authors found progressively decreasing blood
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35 251 oxygen saturations over the first three dialysis sessions in the cohorts that progressed to
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37 252 future hospital admission or death (9). This finding is replicated in our study, where
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39 253 hypoxia was evident at the second presentation of patients who had satisfactory vital
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41 254 parameters a few days earlier.

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43 255 In the transplantation cohort, there have been few reports of successful
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45 256 management of patients as outpatients, through a systematic strategy to triage out-patient
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47 257 and in-patient care. In one study, symptomatic resolution was achieved without the need
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5 258 for hospitalization, through early management of bacterial infections and minor
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7 259 adjustment of immunosuppression (13,14).
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9 260 The 28-day mortality of KRT recipients has been reported in published literature
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11 261 to vary from 15% to 29% (13-15). This corresponds with the 28-day mortality for
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13 262 patients hospitalized at the first (29%) and at the second presentation (25%) in our study.
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15 263 Patients who did not return for a second presentation had a 28-day mortality of 6%. The
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17 264 causes of death in the latter instances are not known. In a large study from a major
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19 265 healthcare system in the United States, mortality of patients with COVID-19, was
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21 266 predicted by a three-variable prediction model. These were older age, low oxygen
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23 267 saturation during the encounter and the type of encounter (inpatient vs outpatient vs
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25 268 telehealth). In this dataset, patients who were alive were more likely to have had their
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27 269 initial encounter at a hospital than at an outpatient or telehealth setting within that
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29 270 healthcare system than were patients who died (Odds Ratio 15.59, $p < 0.0001$) (16). This
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31 271 reinforces the need for close follow-up of patients, if they are deemed to be safe for
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33 272 discharge at their first consultation, especially if they have co-morbidities.
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39 273 The key strength of our study is that it was performed in real-life conditions
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41 274 during the first wave of the pandemic, with access to complete sociodemographic and
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43 275 clinical datasets from multiple centers, including hospital admission data such as
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45 276 laboratory reports, diagnostic imaging and COVID-19 treatment data. Consequently, this
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47 277 has allowed us to analyze the risk of hospital admission related to COVID-19 adjusted for
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49 278 confounders, thus minimizing possible bias. Our data highlights that supported outpatient
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51 279 care of patients on kidney replacement therapy is a viable management proposition for
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53 280 healthcare institutions. Although the reported prognosis predictors are not modifiable,
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5 281 knowing them can help us prioritize initial and follow-up care for these ‘at-risk’ patient
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7 282 groups. Our study has its limitations. The lack of availability of widespread antigen or
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9 283 antibody testing during the first wave of the pandemic, the extent of disease transmission
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11 284 was not entirely clear leading to the possibility of reporting bias as some patients may
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14 285 have had mild symptoms and may not have presented to the hospital for evaluation. This
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16 286 is especially true for transplant recipients. More detailed virology data with strain types
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18 287 and viral load may have added strength to the prognostication criteria but were
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21 288 unavailable at the time. The study did not collect any center-specific protocols for
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23 289 referrals, admissions or discharges. However, the median time between first and second
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25 290 visit was 5 days (interquartile range: 2-7 days) with worsening of disease symptoms in
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28 291 those who returned for a second visit (Table 2). Therefore, it seems unlikely that centers
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30 292 would have adopted protocols to discharge or arrange re-visits to hospitals on an elective
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32 293 basis during the pandemic. Second presentations were determined mainly by disease
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34 294 symptoms and severity.

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37 295 Balancing safe patient care needs with available resources remains priority as we
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39 296 encounter current and subsequent waves of the pandemic. This study provides insights
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41 297 for further strategies that clinicians may develop and use when caring for outpatient
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43 298 kidney transplant and dialysis recipients. As with other illnesses, individual patient
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46 299 circumstances and clinical judgement must be factored into the decision to admit or not to
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48 300 admit to the hospital.

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AUTHORS' CONTRIBUTIONS

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

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The ERACODA collaboration is an initiative to study prognosis and risk factors for mortality due to COVID-19 in patients with a kidney transplant or on dialysis that is endorsed by the ERA-EDTA. ERACODA is an acronym for European Renal Association COVID-19 Database. The organizational structure contains a Working Group assisted by a Management Team and Advisory Board.

The ERACODA Working Group members: Franssen CFM, Gansevoort RT (coordinator), Hemmelder MH, Hilbrands LB and Jager KJ.

The ERACODA Management Team members: Duivenvoorden R, Noordzij M, Vart P.

The ERACODA Advisory Board members: Abramowicz D, Basile C, Covic A, Crespo M, Massy ZA, Mitra S, Petridou E, Sanchez JE, White C.

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DATA AVAILABILITY STATEMENT

Collaborators that entered data in ERACODA remain owner of these data. The database 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

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5 324 journals when requested. Research proposals can be submitted to the Working Group via
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7 325 COVID.19.KRT@umcg.nl. If deemed of interest and methodological sound by the
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9 326 Working Group and Advisory Board, the analyses needed for the proposal will be carried
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11 327 out by the Management Team.
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13

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19 333 **CONFLICT OF INTEREST STATEMENT**

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27 336 relevant conflicts of interest to declare.
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386 **Table 1. Characteristics of all patients at First Presentation stratified according to**
 387 **their hospital admission status**

	Hospitalization at 1 st presentation			p-value	Not hospitalized at 1 st presentation (n=355)		p-value
	Total N=1,423	Yes N=1,068	No N=355		Returned for 2 nd presentation N=36	Did not return for 2 nd presentation N=319	
Patient characteristics							
Male sex, %	61	62	56	0.06	64	55	0.33
Age, year	64 ± 15	64 ± 14	64 ± 16	0.53	72 ± 14	63 ± 16	0.002
Body mass index, kg/m ²	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	
Clinical frailty scale, AU	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
Auto-immune disease, %	5	5	4	0.31	8	3	0.11
Primary kidney disease							
Prim. 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
Sec. 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

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Unknown, %	10	11	8	0.09	6	8	0.63
Dialysis (yes), %	71	67	85	<0.001	78	86	0.19
Haemodialysis, %*	99	99	99	0.29	100	99	0.57
Peritoneal dialysis, %*	1	1	1	0	0	1	
Res. diuresis \geq 200 ml/day, %*	32	33	31	0.002	46	29	0.006
Transplant waiting list status*				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**				0.12			0.04
<1 year, %	7	8	2		0	13	
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	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
Diarrhea, %	16	18	11	<0.001	14	10	0.008
Myalgia or arthralgia, %	21	23	16	<0.001	26	15	0.003
Vital signs							
Temperature, °C	37.5 \pm 1.1	37.6 \pm 1.1	37.2 \pm 1.0	<0.001	37.3 \pm 1.2	37.2 \pm 1.0	0.55
Respiration rate, /min	20 \pm 6	20 \pm 6	17 \pm 4	<0.001	17 \pm 4	17 \pm 3	0.85
O2 saturation room air, %	94 \pm 6	93 \pm 6	97 \pm 3	<0.001	97 \pm 3	97 \pm 3	0.60
SBP, mm Hg	135 \pm 25	135 \pm 25	137 \pm 24	0.14	129 \pm 22	139 \pm 25	0.04
DBP, mm Hg	75 \pm 15	76 \pm 15	73 \pm 15	0.05	69 \pm 15	74 \pm 15	0.07
Pulse rate, BPM	84 \pm 16	85 \pm 16	77 \pm 13	<0.001	73 \pm 11	77 \pm 14	0.13
Laboratory test results							
Creatinine increase (>25%)**	30	33	8	<0.001	25	12	0.007
Lymphocytes, x1000/ μ L	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	31 (8, 84)	38 (10, 95)	13 (3, 43)	<0.001	26 (6, 58)	12 (2, 36)	0.02

388 Continuous variables are reported as mean \pm SD or median (IQR). Groups were compared using Student-t, Wilcoxon or
389 Chi-square test as appropriate. Obesity is defined as BMI $>$ 30 kg/m². *Abbreviations are:* AU, arbitrary units; CT,
390 computerized tomography; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body
391 mass index; °C, degree Celsius; O2, oxygen; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPM, beats
392 per minute; CRP, C-reactive protein.

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393 *in dialysis patients only
394 **in transplant recipients only

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

	Patient characteristics by presentation		p-value
	First presentation N=36	Second presentation N=36	
Characteristics			
Patient identification			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
Diarrhea, %	14	25	0.16
Myalgia or arthralgia, %	26	25	0.71
Vital signs			
Temperature, °C	37.3 ± 1.2	37.6 ± 0.9	0.19
Respiration rate, /min	17 ± 4	23 ± 9	0.003
O2 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%)**	25	62	0.001
Lymphocytes, x1000/μL	0.7 (0.5, 1.1)	0.7 (0.4, 0.9)	0.02
CRP, mg/L	26 (6, 58)	73 (21, 151)	<0.001

398 Continuous variables are reported as mean ± SD or median (IQR). Groups were compared using Student-t, Wilcoxon or
 399 Chi-square test as appropriate. °C, degree Celsius; O2, oxygen; SBP, systolic blood pressure; DBP, diastolic blood
 400 pressure; BPM, beats per minute; CRP, C-reactive protein.

401 **in transplant recipients only

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

	Admitted after first presentation N=1,068	Admitted after second presentation N=34	p-value
Patient Characteristics			
Male sex, %	62	62	0.97
Age, year	64 ± 14	71 ± 14	0.005
Body mass index, kg/m ²	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	
Clinical frailty scale, AU	3.7 ± 1.8	4.0 ± 1.7	0.34
Patient identification			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			0.77
Positive	92	91	
Negative	5	6	
Intermediate/Unknown	2	3	
Abnormality on X-ray (yes)	44	15	0.002
Abnormality on CT scan (yes)	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
Auto-immune 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
Sec. 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
Haemodialysis, %*	99	100	0.73

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Peritoneal dialysis, %*	1	0	
Residual diuresis ≥ 200 ml/day*	33	48	0.08
Transplant waiting list status*			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**			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
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	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
Diarrhea, %	18	15	0.37
Myalgia or arthralgia, %	23	27	0.28
Vital signs			
Temperature, °C	37.6 \pm 1.1	37.4 \pm 1.2	0.21
Respiration rate, /min	20 \pm 6	17 \pm 4	0.006
O ₂ saturation room air, %	93 \pm 6	96 \pm 3	0.003
SBP, mm Hg	135 \pm 25	129 \pm 22	0.19
DBP, mm Hg	76 \pm 15	69 \pm 15	0.009
Pulse rate, BPM	85 \pm 16	74 \pm 11	<0.001
Laboratory test results			
Creatinine increase (>25%)**	33	25	0.52
Lymphocytes, x1000/ μ L	0.9 (0.5, 1.3)	0.7 (0.5, 1.1)	0.42
CRP, mg/L	38 (10, 95)	29 (5, 63)	0.14

406 Continuous variables are reported as mean \pm SD or median (IQR). Groups were compared using Student-t, Wilcoxon or
 407 Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m². *Abbreviations are:* AU, arbitrary units; CT,
 408 computerized tomography; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body
 409 mass index; °C, degree Celsius; CRP, C-reactive protein; DBP, diastolic blood pressure; O₂, oxygen; prim., primary;
 410 SBP, systolic blood pressure.

411 *in dialysis patients only

412 **in transplant recipients only

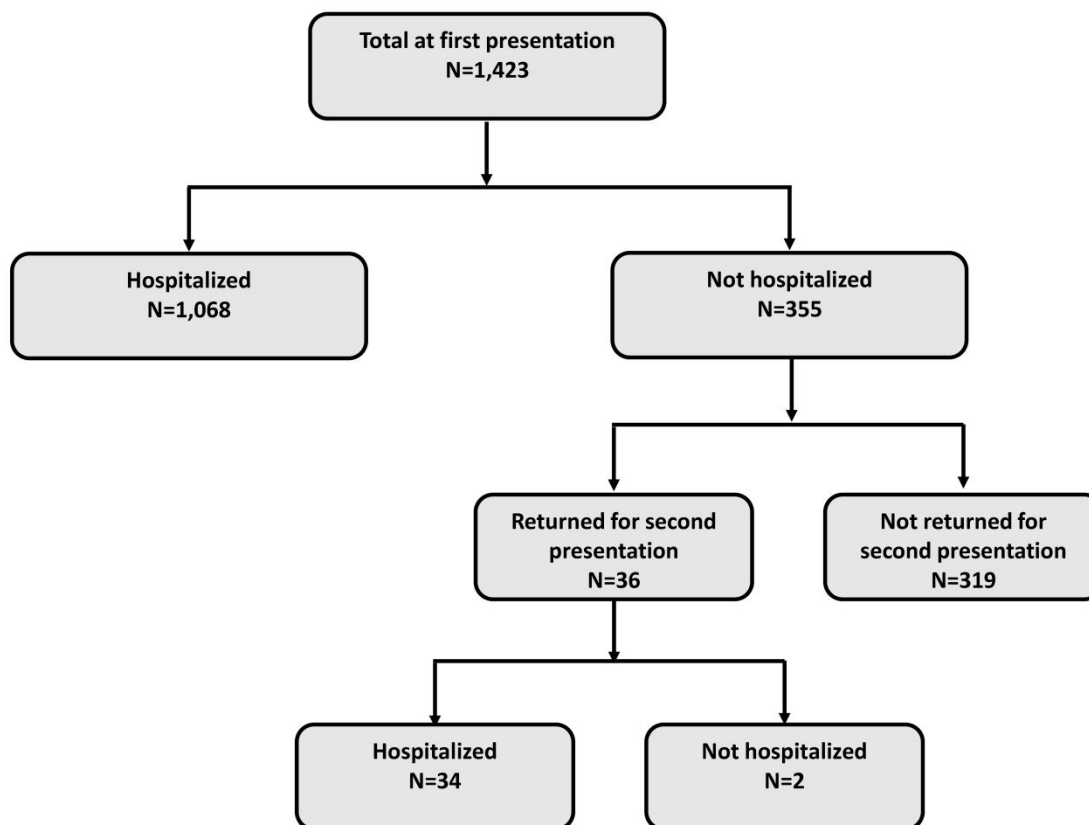
414 **Table 4. Predictors of 28-day mortality in those not admitted to hospital at first**
 415 **presentation (n=355; events=28)** (presented are hazard ratios with 95% confidence
 416 intervals)

	Univariable	p-value	Multivariable	p-value
Patient characteristics				
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 desc	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		
Clinical frailty scale, 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)	-	-		
Body mass index (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		
Auto-immune 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 (vs. transplant)	4.91 (0.67 – 36.15)	0.118		
Days between presentations	two 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		
Diarrhea (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, /minute	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, x1000/μL	1.00 (0.76 – 1.31)	0.99		
CRP, mg/L	1.00 (0.99 – 1.01)	0.36		

417 *Abbreviations are:* AU, arbitrary units; CT, computerized tomography; ACE, angiotensin-converting enzyme; ARB,
 418 angiotensin-II receptor blocker; °C, degree Celsius; CRP, C-reactive protein; O₂, oxygen.

420 **FIGURE 1: Flow chart for patient presentation and hospitalization**

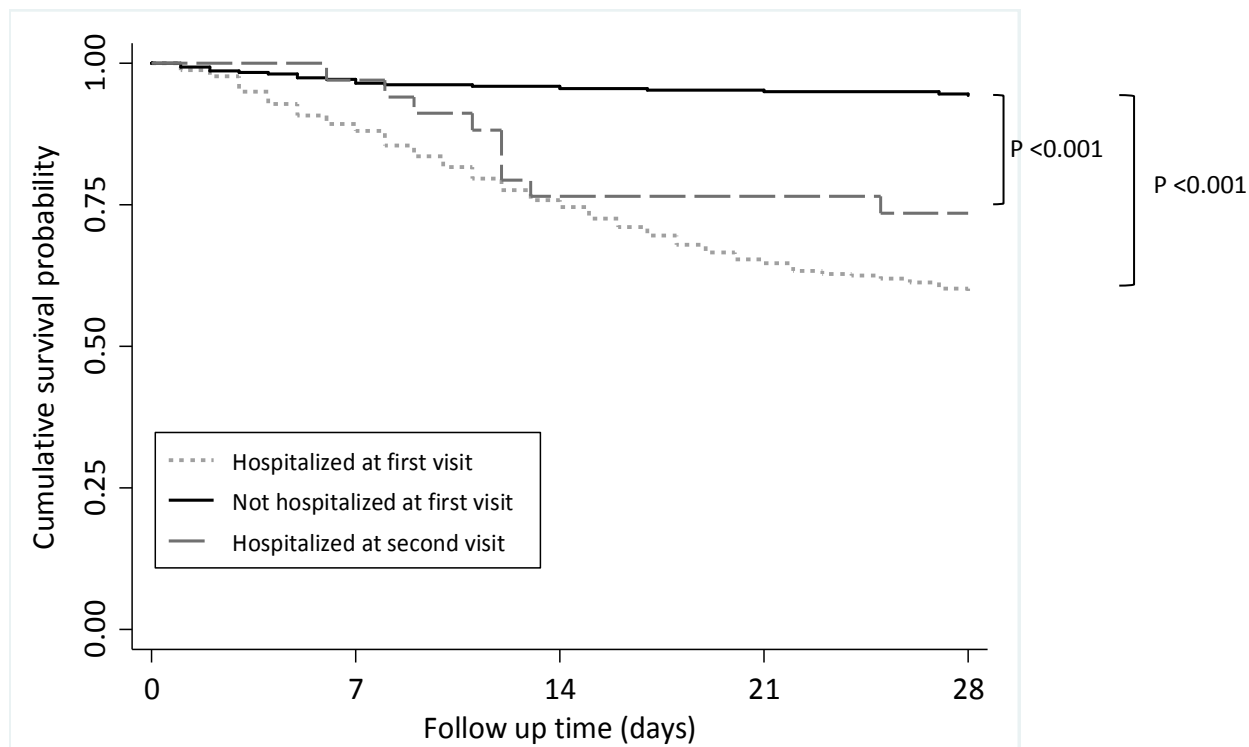
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424 **FIGURE 2: Kaplan-Meier survival curves for 28-day mortality (from date of first**
 425 **presentation) ***
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 428 **1. Hospitalized at first visit**=hospitalized at first visit excluding those who were admitted also on second visit
 429 (n=1089, events=314)
 430 **2. Not hospitalized at first visit**=Not admitted on first and did not return for second visit (n=319, events=19)
 431 **3. Hospitalized at second visit**= Not admitted on first but returned for a second visit and hospitalized (n=34, events=9)
 432 *P-value=0.61 for cumulative survival difference between 1 and 3, and p<0.001 for survival difference between 1 and
 433 2 and 2 and 3

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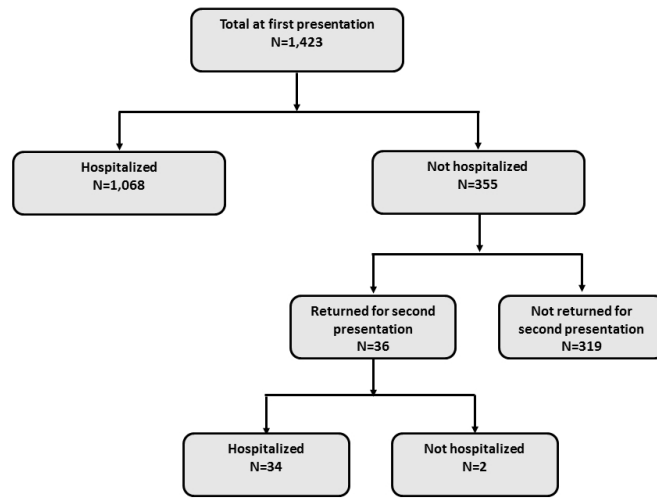


Figure 1

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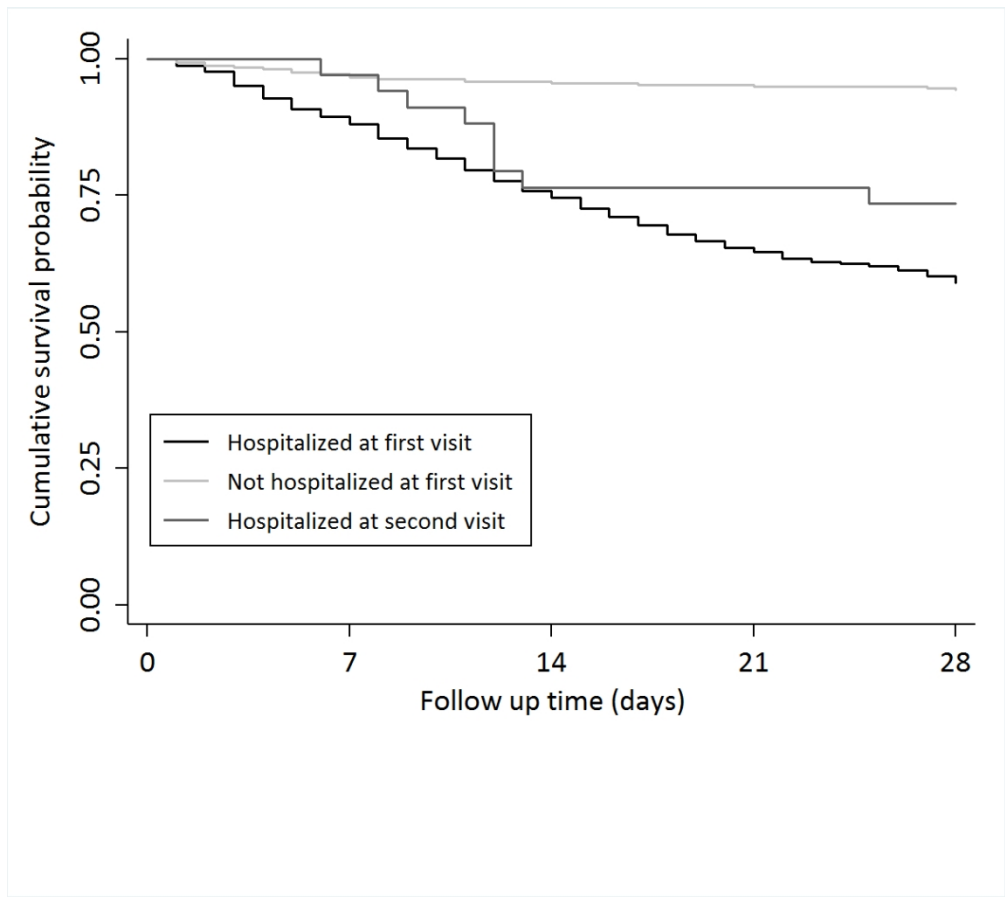


Figure 2

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