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

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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

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

The study informs the outcomes predictors on 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 severity can be managed when presenting to hospitals.

What impact this may have on practice or policy?

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

INTRODUCTION

The COVID-19 pandemic has caused devastation to human lives and major disruption of health care systems and individual patient care 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 SARS-CoV-2, these patients often require high intensity care and major utilization of hospital resources. During the ongoing pandemic, the optimal care pathway and triaging for KRT patients presenting with varying severity of COVID-19 is unknown.

Whilst 80% of patients with COVID-19 have mild symptoms, approximately 10–20% of patients can develop severe disease (2). Understanding of the factors associated with progression of symptoms from the asymptomatic- stage through to severe illness is essential for developing efficient and appropriate triage systems. Avoidance of unnecessary hospitalizations, when clinically appropriate and safe, will offer protection of COVID-19 patients from potential exposure to hospital acquired infections, minimize the risk of transmitting COVID-19 infections to others who don't have the illness, 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 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 to moderate disease who are not hospitalized have been scarcely reported in the literature (3). As the pandemic is sustained through 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 patients on KRT affected by COVID-19.

We analyzed the data of patients receiving kidney replacement therapy who presented with COVID-19. Clinical features, laboratory results, and outcome 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 ERACODA database, 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 more than 200 physicians representing 130 centers in 31 countries, mostly in Europe and bordering the Mediterranean Sea. Data were collected on adult (≥18 years old) 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 polymerase chain reaction assay of nasal or pharyngeal swab specimens, and/or compatible findings on computer tomography 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 database is hosted at the University Medical Center 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 (the Netherlands), who deemed the collection and analysis of data exempt from ethics review regarding the Medical Research Involving Human Subjects Act (WMO).

Data collection

For the current study, all patients with COVID-19 diagnosis between February 1st and June 30th, 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 to 9 based on the Clinical Frailty Scale (CFS) (5). The CFS uses clinical descriptors and pictographs to generate a frailty score for a patient, a score of 1 represents very fit and score of 9 represents 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 infrastructural 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 in case of a non-normal distribution. Categorical

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

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

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 (7). 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, auto-immune disease, ACEi/ARB use, type of kidney replacement therapy (dialysis/transplant), COVID-19 related symptoms and vital signs including cough, fever, shortness of breath, headache, diarrhea, nausea/vomiting, temperature, oxygen saturation, respiration rate, pulse rate, lymphocyte count and C-reactive protein. 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 (6).

All analyses were performed using Stata version 14.0 (College Station, TX). A 2-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

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

Second presentation

Thirty-six of the 355 patients (10%) who were not hospitalized at their first assessment, presented themselves for a second time with clinical illness (Table 1). Of these 36 patients, the numbers of transplant and dialysis recipients were 22% (8) and 78% (28), respectively. Amongst the 355 patients who were not hospitalized initially, practical and logistical considerations precluded hospital admission the first time round for 9% of patients who returned for a second assessment compared to 1% of those who did not return. (Table S1). Figure S1 shows the distribution of patients with a second presentation according to their country of residence. Second attendance cases formed ≤5% of the reported cases in each country, except for France where 24% of the reported cases returned for a second assessment (Table S2). The median time interval between the first and second presentation was 5 days (interquartile range: 2 to 7 days) (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%), shortness of breath (22% versus 10%), abnormalities on chest X-ray (14% versus 8%), lower mean systolic blood pressure (129 ± 26 mmHg versus 139 ± 25 mmHg) and a higher median CRP value 26 mg/L [interquartile interval (6, 58)] versus 12 mg/L [interquartile interval (2, 36)] on initial attendance compared to those patients who did not return for a second presentation. In

those identified on first presentation through screening (routine or because of contact), 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 symptoms of 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 beats/minute to 78 beats/minute). Temperature and blood pressure did not change significantly between first and second presentations (Table 2). An increase in CRP (from 26 mg/L to 73 mg/L) was also noted at their deferred presentation.

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

Compared to patients admitted after their initial consultation, those who were admitted later, were older, more often had prior tobacco use, less often had shortness of breath and fever, had a lower respiratory rate, a higher oxygen saturation, a lower diastolic blood pressure and heart rate and less often had an abnormality on chest x-ray or CT scan at the time of their initial assessment (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 re-admission, whereas 19 of 319 patients (6%) died who were not hospitalized initially but also did not return for a second assessment.

Mortality rate in those who were hospitalized at the deferred admission did not differ from that of the rate in patients who were admitted at their first presentation (p=0.61). However, mortality rate was higher amongst patients who were not hospitalized at first visit and did not return for re-assessment (p<0.001) (Figure 2). Mortality also did not differ between those who were hospitalized at first presentation and those who returned second presentation (29% vs. 25%, p=0.60). Amongst those who had delayed hospital admission, all 9 deaths occurred in hemodialysis patients. RRT modality as dialysis or transplant did not appear as a strong predictor in the multivariate model.

Predictors of prognosis in those not admitted at first presentation.

Higher age, prior tobacco use, higher clinical frailty score, auto-immune 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). Higher age, prior tobacco use, and increase of shortness of breath were identified as predictors of deferred hospital attendance (Table S3) and hospital admission at their second assessment. (Table S4).

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

in patients not hospitalized after initial presentation. Older age and frailty were previously recognized as predictors of hospitalization of hemodialysis 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 out-patient monitoring of the vulnerable KRT patients.

Safety of the out-patient management of the general population with COVID-19 illness, after presenting in Emergency Departments (ED), have been primarily examined in patients who are typically young and not multi-morbid as is the dialysis cohort(11). In these low-risk patients, a minority would require hospitalization after being discharged home from the ED. The ED revisits occurred for 13.7% of patients which is almost similar as in our study. The inpatient admission rate at 30 days was 4.6%, with 0.7% requiring intensive care (11). Increasingly, the importance of early out-patient care of COVID-19 patients is gathering pace, 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 largely to reduce spread of communicable diseases outside 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 re-purposed immunomodulatory and anti-viral drugs

are in development or in trials to help facilitate out-patient 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% vs 21%), suggesting a potential lag before the evolution of symptoms in the hemodialysis cohort. This may be due to potentially earlier identification of hemodialysis patients compared to transplant patients as a larger proportion of cases in hemodialysis were identified through routing screening. Alternatively, this could also imply a lower threshold for admission for home-based transplant patients in contrast to HD patients who attend for incentre dialysis routinely. In a publication from Spain, which reported on the course of a small cohort of hemodialysis 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 hemodialysis recipients has been reported in another study by Medjeral-Thomas et al. 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 few reports of successful management of patients as outpatients, through a systematic strategy to triage out-patient and in-patient care. In one study, symptomatic 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 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 at 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 United States, 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 vs outpatient vs telehealth). In this dataset, patients who were alive were more likely to have had their initial encounter at a hospital than at an outpatient or telehealth setting within that healthcare system than were 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 co-morbidities.

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 centers, including hospital admission data such as laboratory reports, diagnostic imaging and COVID-19 treatment data. Consequently, this has allowed us to analyze the risk of hospital admission related to COVID-19 adjusted for confounders, thus minimizing possible bias. Our data highlights that supported outpatient care of patients on kidney replacement therapy 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, the extent of disease transmission was not entirely clear leading to the possibility of reporting bias as some patients may have had mild symptoms and may not have presented 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 center-specific protocols for referrals, admissions or discharges. However, the median time between first and second visit was 5 days (interquartile range: 2-7 days) with worsening of disease symptoms in those who returned for a second visit (Table 2). Therefore, it seems unlikely that centers would have adopted protocols to discharge or arrange re-visits to hospitals on an elective basis during the pandemic. Second presentations were determined mainly by disease symptoms and severity.

Balancing safe patient care needs with available resources remains priority as we encounter current and subsequent waves of the pandemic. This study provides insights for further strategies that clinicians may develop and use 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.

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.

We thank all people that entered information in the ERACODA database for their participation, and especially all healthcare workers that have taken care of the included COVID-19 patients.

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

journals when requested. Research proposals can be submitted to the Working Group via COVID.19.KRT@umcg.nl. If deemed of interest and methodological 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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CONFLICT OF INTEREST STATEMENT

Mitra S research is supported by the National Institute for Health Research (NIHR) infrastructure at Manchester and D4D MIC Sheffield, UK. The other authors have no relevant conflicts of interest to declare.

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Table 1. Characteristics of all patients at First Presentation stratified according to their hospital admission status

		Hospitalization at 1st presentation			Not hospitalized at 1st presentation (n=355)		
	Total N=1,423	Yes N=1,068	No N=355	p-value	Returned for 2nd presentation N=36	Did not return for 2nd presentation N=319	p-value
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

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	1	
Res. diuresis ≥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 ± 1.1	37.6 ± 1.1	37.2 ± 1.0	<0.001	37.3 ± 1.2	37.2 ± 1.0	0.55
Respiration rate, /min	20 ± 6	20 ± 6	17 ± 4	<0.001	17 ± 4	17 ± 3	0.85
O2 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%)**	30	33	8	<0.001	25	12	0.007
Lymphocytes, x1000/µL	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

Continuous variables are reported as mean ± SD or median (IQR). Groups were compared using Student-t, Wilcoxon or Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. *Abbreviations are:* AU, arbitrary units; CT, computerized tomography; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; °C, degree Celsius; O2, oxygen; SBP, systolic blood pressure; DBP, diastolic blood pressure; BPM, beats per minute; CRP, C-reactive protein.

*in dialysis patients only
**in transplant recipients only

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

	Patient characteristics by presentation		
	First presentation N=36	**Second presentation N=36**	**p-value**
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

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

**in transplant recipients only

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

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 ± 1.1	37.4 ± 1.2	0.21
Respiration rate, /min	20 ± 6	17 ± 4	0.006
O2 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%)**	33	25	0.52
Lymphocytes, x1000/µL	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

Continuous variables are reported as mean ± SD or median (IQR). Groups were compared using Student-t, Wilcoxon or Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. *Abbreviations are:* AU, arbitrary units; CT, computerized tomography; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; °C, degree Celsius; CRP, C-reactive protein; DBP, diastolic blood pressure; O2, oxygen; prim., primary; SBP, systolic blood pressure.

*in dialysis patients only

**in transplant recipients only

Table 4. Predictors of 28-day mortality in those not admitted to hospital at first presentation (n=355; events=28) (presented are hazard ratios with 95% confidence 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 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		
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		
O2 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		

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

FIGURE 1: Flow chart for patient presentation and hospitalization

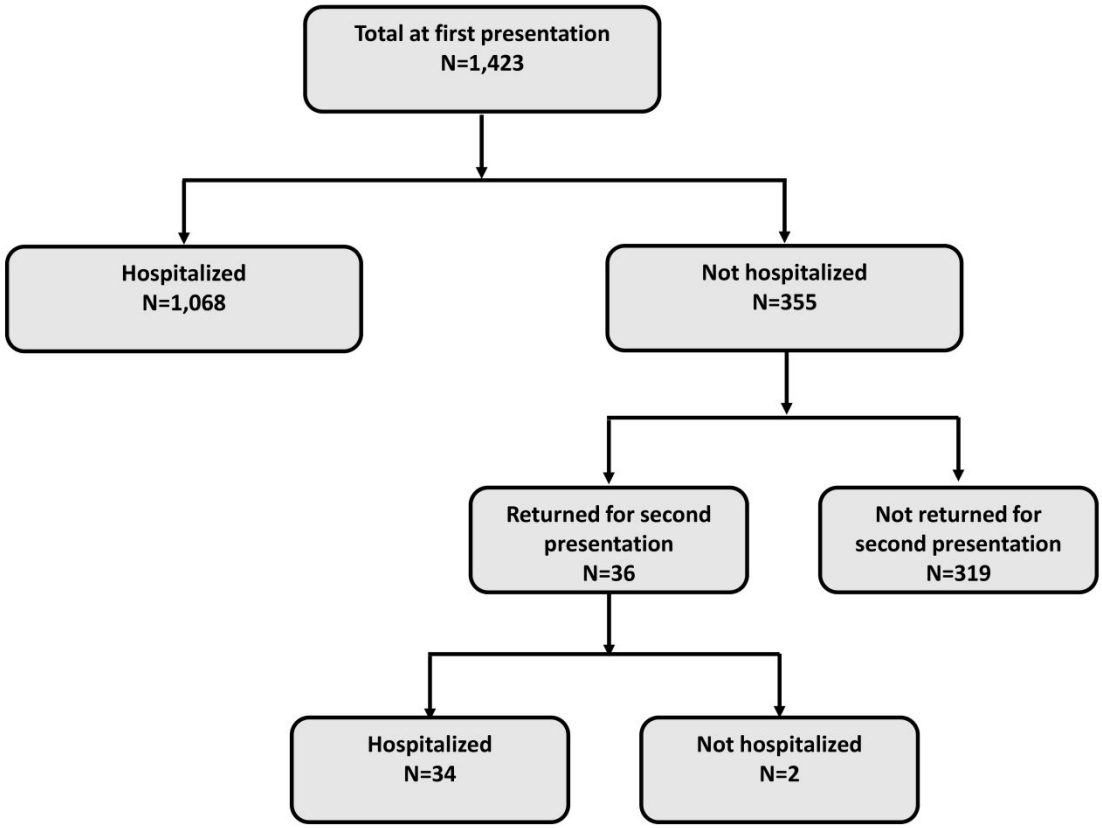
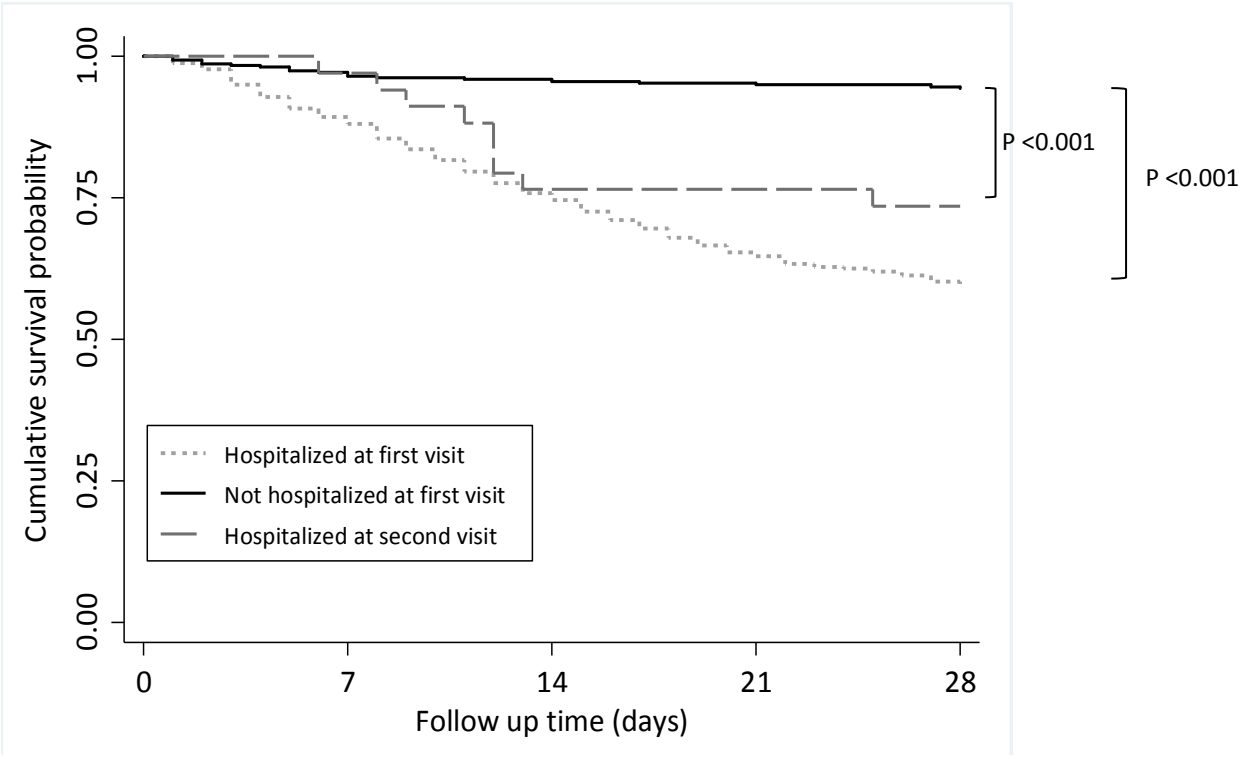


FIGURE 2: Kaplan-Meier survival curves for 28-day mortality (from date of first presentation) *



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 and did not return for second visit (n=319, events=19)

3. Hospitalized at second visit= Not admitted on first 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

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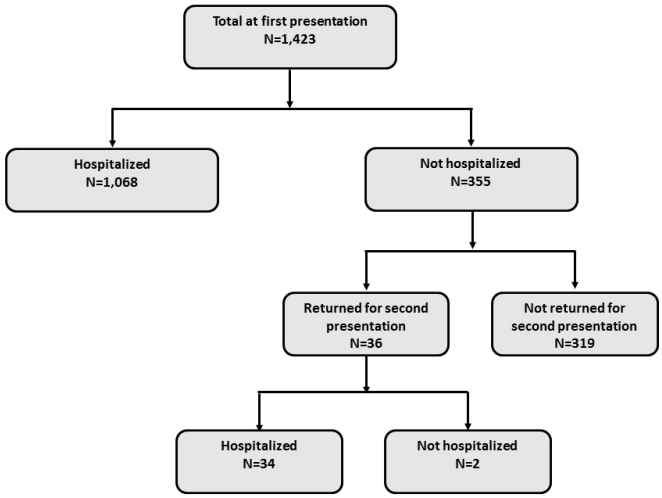

Figure 1

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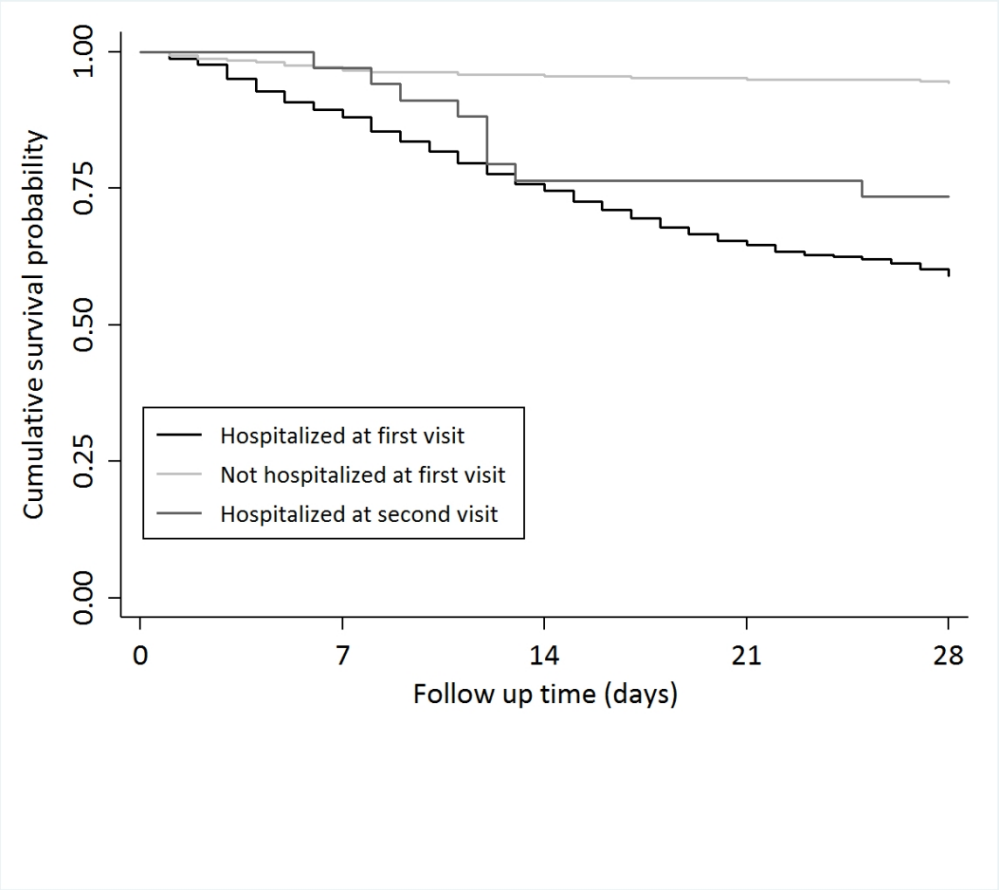

Figure 2

423x376mm (72 x 72 DPI)