Clinical characteristics and outcome of critically ill COVID-19 patients with Acute Kidney Injury: A single centre cohort study

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Research Article

Keywords: COVID-19, Intensive care, Acute kidney injury

Posted Date: July 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40934/v1

Version of Record: A version of this preprint was published at BMC Nephrology on March 15th, 2021. See the published version at https://doi.org/10.1186/s12882-021-02296-z.

Abstract

Background

Acute kidney injury (AKI) is a common manifestation among patients critically ill with SARS-CoV-2 infection (Coronavirus 2019) and is associated with significant morbidity and mortality. The pathophysiology of renal failure in this context is not fully understood, but likely to be multifactorial. The intensive care unit outcomes of patients following COVID-19 acute critical illness with associated AKI have not been fully explored. We conducted a cohort study to investigate the risk factors for acute kidney injury in patients admitted to and intensive care unit with COVID-19, its incidence and associated outcomes.

Methods

We reviewed the medical records of all patients admitted to our adult intensive care unit suffering from SARS-CoV-2 infection from 3rd March 2020 until 10th May 2020. Acute kidney injury was defined using the Kidney Disease Improving Global Outcome (KDIGO) criteria. The outcome analysis was assessed up to date as 15th of June 2020.

Results

A total of 81 patients admitted during this period. All patients had acute hypoxic respiratory failure and needed either noninvasive or invasive mechanical ventilatory support. Thirty-six patients (44%) had evidence of AKI (Stage I-33%, Stage II-22%, Renal Replacement Therapy (RRT)-44%). All patients with AKI stage III had RRT. Age, diabetes mellitus, immunosuppression, lymphopenia, high D-Dimer levels, increased APACHE II and SOFA scores, mechanical ventilation and use of inotropic or vasopressor support were significantly associated with AKI. The peak AKI was at day 4 and mean duration of RRT was 9 days. The mortality was 25% for the AKI group compared to 7% in those without AKI. Among those received RRT and survived their illness, the renal function recovery is complete and back to baseline in 92% of patients.

Conclusion

Acute kidney injury and renal replacement therapy is common in critically ill patients presenting with COVID-19. It is associated with increased severity of illness on admission to ICU, increased mortality and prolonged ICU and hospital length of stay.

Introduction

SARS-CoV-2 viral infection leading to Coronavirus 2019 (COVID-19) was declared as an emerging pandemic by the World Health Organization (WHO) in March 2020 [1]. The first case was reported in the

United Kingdom (UK) on the 31st January and patient numbers rose rapidly with a corresponding increase in admissions to hospital and intensive care units (ICU) over the subsequent months. Although the majority of infected patients developed mild or no respiratory symptoms, a proportion progressed to severe lung disease characterised by acute hypoxic respiratory failure (AHRF) necessitating respiratory support or mechanical ventilation. Acute kidney injury (AKI) in cases of COVID-19 admitted to ICU is well documented. In a study from the United States of America of a cohort of over 5000 patients 36.6% of patients developed acute kidney injury (AKI) according to KDIGO criteria [2]. In the UK, a quarter of patients in intensive care developed AKI requiring renal replacement therapy (RRT) and it was associated with increased mortality [3]. Furthermore, AKI may be associated with an ongoing requirement for renal support and prolonged hospitalization thereby imposing a significant health and resource burden.

The pathophysiology of AKI in COVID-19 is poorly understood but may involve a combination of pre-renal and intrinsic renal insults. Studies have described the virus' affiliation for the angiotensin converting enzyme-2 (ACE-2) receptor, which is expressed in abundance in the kidney [4,5]. The virus also directly infects tubular epithelial cells and podocytes causing significant structural damage [6]. Proteinuria and haematuria have been commonly documented and may be indicative of intrinsic renal injury [2,7,8]. Post-mortem findings of COVID-19 patients suggest micro-vascular occlusion, endothelial injury, diffuse acute proximal tubular injury and evidence of direct damage as a consequence of SARS CoV-2 infection [6].

The majority of critically ill patients with COVID-19 require ventilatory support, but the clinical manifestations of COVID-19 vary and the characteristics and outcomes of patients with AKI have not been fully defined. Consequently we aimed to characterise the risk factors for AKI in intensive care patients with Covid-19, its incidence and patient outcomes in a single centre cohort study.

Methods

This study was conducted in a General Intensive Care Unit (GICU) at the University Teaching Hospital in Southampton (UHS), UK. All adult patients (>18 years old) admitted between 03/03/2020 and 10/05/2020 with a diagnosis of COVID-19 confirmed via a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) test were included in this study. The respiratory samples were taken from nasal and throat swabs or endotracheal tube aspirates for confirmatory analysis. Ethical approval was obtained as part of the REACT COVID observational study (A longitudinal Cohort Study to facilitate Better understanding and Management of SARS-CoV-2 infection from hospital admission to discharge across all levels of care): REC Reference 17/NW/0632 SRB Reference Number; SRB0025. Due to the nature of the study, the need for individual informed consent was waived.

Data was collected from an electronic clinical record system (*Meta-vision, iMDsoft*). This included baseline demographics, past medical history, pre-hospital medication, timings of disease onset, laboratory test results, ventilator strategies and clinical information regarding renal supportive measures and outcomes. Comorbidities included; diabetes mellitus, ischæmic heart disease, hypertension, chronic kidney disease, immunosuppression and congestive cardiac failure. We further quantified the severity of

comorbidities using the Charlson's comorbidity index [9]. Disease severity on admission to the ICU was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score and degree of hypoxia from the ratio of arterial oxygen partial pressure (PaO_2 in kPa) to fractional inspired oxygen (PaO_2/FiO_2 ratio or P/F ratio).

Acute kidney injury was defined based by the Kidney Disease Improving Global Outcome (KDIGO) classification which depends on the serum creatinine profile during the hospital admission [10]. Briefly, stage I is classified when 1.5-1.9 times, stage II 2.0-2.9 times (or ³26.5 mmol/l increase) and stage III 3 times increment (or ³353.6 mmol/l increase or initiation of renal replacement therapy) from the baseline serum creatinine when available. If creatinine was found to be elevated at presentation, we reviewed the case notes for historical results within one year to determine if this was an acute process. If there were no historical blood results, then an estimated baseline creatinine was used to grade the AKI according to their gender, ethnicity and age (according to KDIGO criteria) [10]. Renal function recovery is defined as improvement in creatinine below 1.5 times the baseline or estimated creatinine. All admitted patients were divided into two groups; patients with AKI and without AKI.

Descriptive statistics were used to characterize the clinical variables of patients in the AKI and no AKI groups. The Kolmogorov-Smirnov was used to evaluate normality in continuous data. Direct comparisons between the AKI and no AKI groups were performed with the Mann-Whitney U (continuous variables) and Fisher's exact tests (categorical variables).

Results

Between 4th of March and 12th of May 2020, a total of 81 critically ill COVID-19 patients were admitted to the Intensive Care Unit. The median age was 57 (IQR 18) and 62% were male. The median duration of symptoms prior to hospitalisation was 7 days (IQR 5). 56.8% were white and 48.1% had a raised BMI of ³30kg/m^2. Chronic kidney disease was evident in 5 patients (6.2%) and one patient was receiving long-term dialysis for end stage renal failure secondary to diabetic nephropathy. The comorbidities recorded were diabetes mellitus (25.9%), hypertension (37%) and immunosuppression (9.9%). Of patients with immunosuppression; 3 patients had Human Immunodeficiency Virus infection (HIV), 2 had hematological malignancies, 2 were on immunosuppressive medications for autoimmune diseases and one undergoing chemoradiotherapy for intracerebral solid tumor. Twenty patients (24.7%) were documented to be on prescription medication of either an angiotensin converting enzyme II (ACE II) inhibitor or an angiotensin receptor blocker (ARB).

Thirty-six patients (44.4%) had an AKI during their ICU stay. Of these, 12 (33.3%) had AKI stage I, 8 (22.2%) had AKI stage II and 16 patients (44.5%) had AKI stage III and received renal replacement therapy (RRT) (Fig. 1).

The patients with AKI were older (61 vs 50, p=0.0071) with increased comorbidities as quantified by Carlson's comorbidity index (2.5 vs 1, p=0.0016) and had a higher incidence of diabetes mellitus (38.9%

vs 15.6%, p=0.0225) and immunosuppression (19.4% vs 2.2%, p=0.0193) (Table 1). Patients with AKI had greater illness severity as determined by APACHE II (20 vs 12, p<0.0001) and SOFA (5 vs 3, p=0.0001) scores. The degree of acute hypoxic respiratory failure was similar in the two groups: PaO_2/FiO_2 ratio (P/F ratio) of 14.4 vs 15.4 kPa, p=0.0811). However, AKI patients were more likely to have received invasive mechanical ventilation (86.1% vs 37.8%, p=0.0001) and vasopressor or inotropic support (91.7% vs 35.6%, p=0.0001). The use of diuretics and corticosteroids were also more common in patients with AKI. The clinical characteristics of all patients are presented in Table 1.

On admission, patients with AKI had lower lymphocyte counts and higher D-Dimer, troponin and creatinine levels (Table 1). The lymphopenia with raised levels of D-Dimers persisted even at day 7. In patients without AKI, lymphocyte count increased following ICU admission (Fig. 2).

For patients admitted to ICU with AKI, the median time from (we calculated from ICU admission) to documented peak AKI was 4 days (IQR 6 days). For patients who received RRT, the median time to commencing RRT was 5 days (IQR 6 days) after admission to the intensive care unit and the median duration of RRT was 9 days (IQR 11 days). The mode of renal support was primarily continuous veno-venous hemodiafiltration (CVVHDF) with citrate anticoagulation. Out of the 16 patients who received RRT, 10 received additional formal therapeutic anticoagulation with intravenous heparin.

Outcomes are up to date as of June 15th, 2020. Among those patients with AKI and survived the acute illness, 96.3% (26/27) have fully recovered to their baseline renal function. One patient remains in intensive care requiring continuous RRT and another continues with long term planned dialysis after ICU discharge (Fig. 3). The overall hospital mortality for the patients admitted to ICU with AKI was 25% (9/36), compared to 6.7%, (3/45) in those without AKI. Eight patients are still hospitalised (all from the AKI group) and three of these patients still remains in ICU; one requiring RRT and 2 with ongoing respiratory rehabilitation (Table 2). For those completed cases, the median length of ICU and hospital stay was significantly longer in patients with AKI at 23.5 (IQR 35) and 27 days (IQR 23) compared to 5.5 days (IQR 11) and 15.5 days (IQR 14 days) for without AKI, respectively.

Discussion

In this study, we report that 45% of COVID-19 patients admitted to intensive care for respiratory support developed an AKI and 20% required renal replacement therapy acutely for an average duration of 9 days. Overall hospital mortality for critically ill ICU patients with COVID-19 was 15%, compared to 25% in patients with AKI. All patients with AKI stage I and II had complete recovery to their baseline renal function and 92% of those who received RRT and survived had no ongoing requirement for RRT. Risk factors for the development of AKI were older age, preexisting diabetes mellitus and immunosuppression. AKI was associated with increased disease severity on admission (APACHE II and SOFA scores), persistently raised D-Dimer and more severe lymphopenia.

AKI is an independent risk factor for increased mortality in all critical illness [11,12]. The reported incidence of AKI among critically ill COVID 19 patients in other cohorts is approximately 20-30% and it is regarded as a marker of disease severity [13,14]. Reports from the USA and the UK suggest renal replacement rates of 25-31% in critically ill COVID-19 patients [3,15]. The incidence of AKI in our cohort was higher (44%) with 20% requiring renal replacement therapy.

Our finding of increased mortality in patients with AKI (25% vs 6.7%) is in keeping with other COVID-19 case cohorts [7,8,16,17]. Patients with AKI had more severe illness generally, required invasive mechanical ventilation, had higher illness severity scores, persistent lymphopenia and vasopressor support, suggesting that AKI is a marker of disease severity. Of our AKI completed cases that have been discharged home (n=28), mortality for all the AKI groups, Stage I, Stage II and the RRT group are 33%, 28.5% and 33% respectively. This is lower than the 60% national mortality in patients receiving RRT reported in the UK ICNARC outcome dataset [3]. Patients in our RRT cohort had similar age and acute severity indices (APACHE II of 21, PaO_2/FiO_2 15.1kPa) with higher mechanical ventilation rate (100%) and 92% had vasoactive agents as advanced cardiovascular support suggesting this group is comparable to the ICNARC dataset [3].

Although the exact pathophysiological mechanism of AKI in COVID-19 remains elusive, it appears to be multifactorial. The angiotensin converting enzyme II (ACE-II) has been identified as a specific receptor for SARS-CoV-2 viral infection and is found in abundance in renal tubular epithelium and podocytes [18]. Direct viral infection causing proximal tubular injury and disruption to podocytes has been demonstrated in postmortem studies with associated clinically documented presentation of hematuria and proteinuria [6]. Moreover, there is local immune response with lymphocytic and $CD8^+$ macrophage infiltration which may promote tubuloepithelial injury [19].

Hypercoagulability, microthrombi and microvascular injury have been extensively documented in patients with COVID-19 and may contribute to the development of AKI [20]. The contribution of microthrombi formation in AKI has been found in postmortem findings, where there is erythrocyte stagnation with clot formation in the glomerular and peri-tubular capillaries in COVID-19 patients [6]. Moreover, one study demonstrated that elevated D-Dimer level and complete failure of lysis at 30 minutes on a thromboelastogram are predictive of significant increase in the incidence of thromboembolism and a need for haemodialysis in critically ill COVID-19 patients [21]. In our report, the development of AKI was associated with raised admission D-dimer levels and these abnormalities persisted in patients with AKI even after a week of ICU admission. This supports the fore-mentioned studies and highlights this maybe a potential contributor to the underlying pathophysiology of AKI in COVID-19 cases.

Interestingly, the use of diuretics was much more common in patients with AKI. Diuretics are often used in the intensive care setting to enhance a judicious fluid balance to improve oxygenation in patients with acute severe hypoxic respiratory failure. It is not clear whether the increased usage of diuretics contributed to the development of AKI or whether they were used to facilitate urine output and consequently improves fluid balance when AKI was already established. Similarly, AKI patients were more

likely to be treated with corticosteroids. Corticosteroid use probably reflects a more severe disease process and it is not possible to make any direct conclusions regarding cause and effect from this study.

Our study has several limitations. Firstly, this is a small cohort study of patients admitted with COVID-19 characterised by acute hypoxic respiratory failure and needing respiratory support may not be representative of all hospitalised COVID-19 patients. Secondly, the laboratory testing for D-Dimer was not consistently measured for all patients and the missing values may have introduced bias. Moreover, there was an upper limit cutoff for D-Dimer values of 5000mg/l and as a result, we were unable to present the absolute laboratory values for levels beyond >5000mg/l. Thirdly, although our data is up to date as of 15th of June 2020; 22% of patients admitted with AKI remain in hospital so their final outcome is unknown which may impact our mortality estimates. Finally, we did not perform additional renal specific urine biological investigations to characterize the AKI which limits our ability to evaluate the mechanism of renal injury. Whilst we recognise these limitations, we were still able to identify factors associated with the development of AKI and outcome of AKI recovery. Reassuringly, all but one patient who recovered from their acute illness have also completely recovered from their acute kidney injury.

Conclusions

Acute kidney injury is a common feature in critically ill patients with COVID-19 pneumonia presenting with acute hypoxic respiratory failure. It is more common in patients with immunosuppression, hypertension and diabetes. The development of AKI is associated with increased severity of illness, prolonged duration of hospitalisation and increased mortality. Reassuringly, nearly all surviving patients recovered from their AKI.

List Of Abbreviations

ACE: Angiotensin converting enzyme

AHRF: Acute hypoxic respiratory failure

AKI: Acute kidney injury

APACHE II: Acute Physiology and Chronic Health Evaluation II

ARB: Angiotensin receptor blocker

COVID-19: Coronavirus disease 2019

CVVHDF: Continuous veno-venous hemodiafiltration

HIV: Human immunodeficiency virus

ICU: Intensive care unit

KDIGO: Kidney Disease Improving Global Outcome

RRT: Renal replacement therapy

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SOFA: Sequential Organ Failure Assessment

WHO: World Health Organisation

Declarations

Ethics approval and consent to participate

Ethical approval was obtained as part of the REACT COVID observational study (A longitudinal Cohort Study to facilitate Better understanding and Management of SARS-CoV-2 infection from hospital admission to discharge across all levels of care): REC Reference 17/NW/0632 SRB Reference Number; SRB0025. Due to the nature of the study, the need for individual informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available for the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding for the study.

Authors contributions

Conception and design: RL, AJ, RD, and AD

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Tables

Demographics	All patients (N=81)	Patients with AKI (N=36)	Patients without AKI (N=45)	P-value
Age, years	57 (18)	61 (14)	50 (16)	P=0.0071*
Male (%)	62%	66.7%	57.8%	P=0.4930
Symptomatic days prior to hospitalisation	7 (5)	7 (7)	8 (4)	P=0.1183
BMI ≥30 kg/m^2, n (%)	29 (48.1%)	21 (58.3%)	18 (40%)	P=0.1208
Charlson's comorbidity index	2 (2)	2.5 (3)	1(3)	P=0.0016*
Race/ethnic group				
White	46 (56.8%)	24 (66.7%)	22 (48.9%)	P=0.1209
Black	7 (8.6%)	4 (11.1%)	3 (6.7%)	P=0.6941
Asian/Indian	20 (24.7%)	5 (13.9%)	15 (33.3%)	P=0.0684
Other/unknown	8 (9.9%)	3 (8.3%)	5 (11.1%)	P=0.7274
Comorbidities, n (%)				
Chronic kidney disease	5 (6.2%)	3 (8.3%)	2 (4.4%)	P=0.6511
Congestive cardiac failure	4 (4.9%)	2 (5.6%)	2 (4.4%)	P=1.0000
Diabetes mellitus	21 (25.9%)	14 (38.9%)	7 (15.6%)	P=0.0225*
Hypertension	30 (37%)	15 (41.7%)	15 (33.3%)	P=0.4924
Ischemic heart disease	7 (8.6%)	2 (5.6%)	5 (11.1%)	P=0.4537
Immunosuppression	8 (9.9%)	7 (19.4%)	1 (2.2%)	P=0.0193*
Use of ACEi or ARB	20 (24.7%)	10 (27.8%)	10 (22.2%)	P=0.6111
Severity indices				
APACHE II Score	14 (12)	20 (11.2)	12 (6)	P<0.0001*
SOFA Score	4 (3)	5 (3)	3 (1)	P=0.0001*
PaO_2/FiO_2 ratio (kPa)	15 (5)	14.4 (4.5)	15.4 (4.8)	P=0.0811
ICU interventions				
Mechanical ventilation, n (%)	48 (59.3%)	31 (86.1%)	17 (37.8%)	P=0.0001*
Non-invasive ventilation, n (%)	33 (40.7%)	5 (13.9%)	27 (60%)	P=0.0001*
Vasopressor use, n (%)	49 (60.5%)	33 (91.7%)	16 (35.6%)	P=0.0001*
Vasopressor use >1 type, n (%)	15 (18.5%)	13 (36.1%)	2 (4.4%)	P=0.0003*
Diuretics use, n (%)	49 (60.5%)	27 (75.0%)	22 (48.9%)	P=0.0225*
Diuretics use >1 type, n (%)	20 (24.7%)	14 (38.9%)	6 (13.3%)	P=0.0090*
Corticosteroids	23 (28.4%)	15 (41.7%)	8 (17.8%)	P=0.0255*
Pulmonary vasodilators, n (%)	11 (13.6%)	8 (22.2%)	3 (6.67%)	P=0.0544
Antibiotics (any), n (%)	81 (100%)	36 (100%)	45 (100%)	P=1.0000
Antivirals (any), n (%)	25 (31.9%)	12 (33.3%)	13 (28.9%)	P=0.8093
Admission laboratory profile				
Bilirubin (mmol/l)	11 (6)	11 (9)	11 (5)	P=0.8939
Creatinine (mmol/l)	72 (44)	98 (84)	65 (28)	P=0.0222*
Creatinine kinase (U/l)	160 (240)	153 (411)	174 (237)	P=0.8105
C-Reactive Protein (mg/l)	153 (106)	166 (135)	125 (82)	P=0.0598
D-Dimer (mg/l)	527 (742)	942 (2157)	444 (395)	P=0.0318*
Ferritin (mg/l)	965 (1430)	842 (963)	989 (1601)	P=0.9087
HbA1c (mmol/mol)	46 (9)	48 (10)	44.5 (8)	P=0.0615
LDH (U/l)	909 (572)	1026 (721)	909 (550)	P=0.9745
Lymphocytes 10^9/l	0.9 (0.7)	0.700 (0.7)	1.000 (0.6)	P=0.0133*
Procalcitonin (ng/ml)	0.3 (0.6)	0.6 (0.9)	0.3 (0.5)	P=0.1076
HS Troponin (ng/l)	13 (26.5)	27.5 (117)	9 (8)	P=0.0001*
White cell counts 10^9/l	8.2 (6.5)	8.9 (7)	7.6 (5.7)	P=0.2935

Table 1. Patient demographics on admission, disease severity indices, intensive care interventions and admission laboratory markers from all COVID-19 admitted patients. Data are presented as median (Interquartile Range) or numbers (percentage) unless otherwise stated. *P<0.05 as assessed by Fisher's Exact test for categorical variables and Mann-Whitney U test for continuous variables. ACEi, Angiotensin Converting Enzyme inhibitor; APACHE II, Acute Physiology and Chronic Health Evaluation II score; ARB, Angiotensin Receptor Blocker, BMI, Body Mass Index; LDH, Lactate dehydrogenase; HS Troponin, High Sensitivity Troponin; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; SOFA, Sequential Organ Failure Assessment score.

Outcomes	Patients with AKI (N=36)	Patients without AKI (N=45)
Length of RRT	8.5 (10.8)	N/A
Length of ICU Stay	23.5 (35)	5.5 (11)
Length of Hospital Stay	27 (23)	15.5 (14)
Death	9 (25.0%)	3 (6.7%)
Still Hospitalised	8 (22.2%)	0 (0%)
Still in ICU	3 (8.3%)	0 (0%)
Still on RRT	2*	N/A
Discharged Home	19 (52.8%)	42 (93.3%)

Table 2. Outcome of all patients with and without acute kidney injury. AKI, Acute Kidney Injury; ICU, Intensive Care Unit; RRT, Renal Replacement Therapy. Data are presented as median (Interquartile Range) or numbers (percentage) unless otherwise stated. *One patient for AKI and another for CKD with established long-term dialysis programme.

Figures

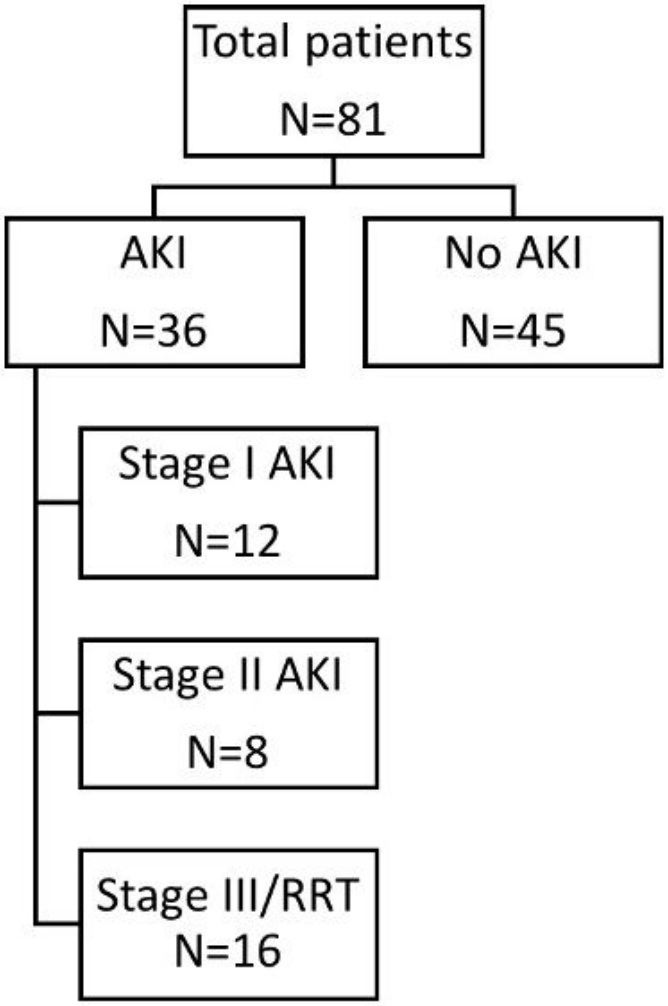

Figure 1

COVID-19 patient flow diagram. AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy. The Acute Kidney Injury is defied according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.

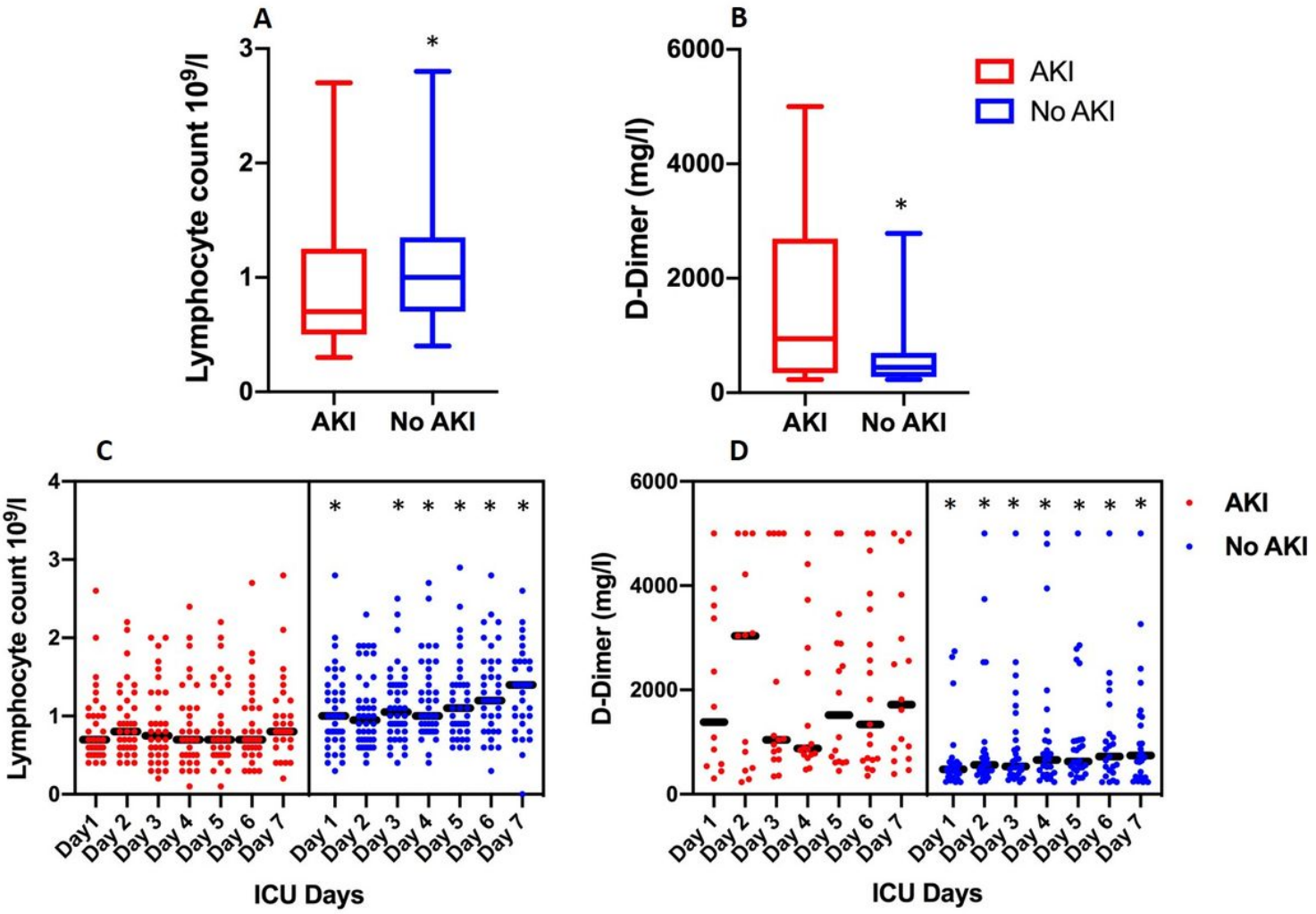

Figure 2

The lymphocyte counts (109/l) and D-Dimer levels for Day 1 (A: lymphocyte, B: D-Dimer) and over the 7 days of Intensive Care Unit admission (C: lymphocyte counts, D; D-Dimer) for both groups with and without acute kidney injury. The 2A and 2B are presented as Box and Whiskers plots with median and maximum and minimum values. 2C and 2D shows scatter plots and the lines represent median values. *The comparison between AKI vs No AKI group for that particular time point by Mann-Whitney U test and $P<0.05$.

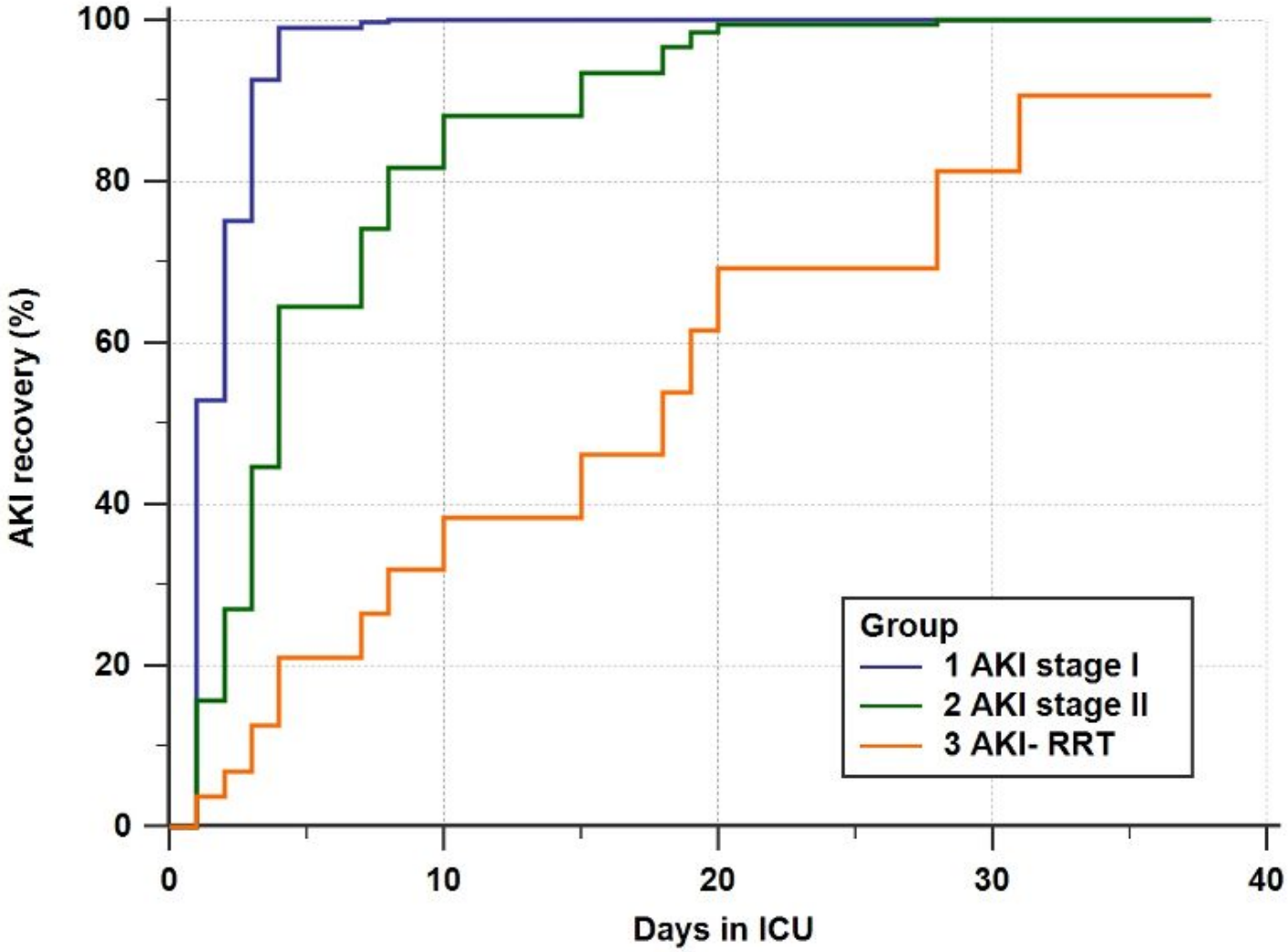

Figure 3

The recovery of acute kidney injury across all stages of AKI as defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria over time during the intensive care unit stay. The RRT group recovery is defined as normalisation of renal function off renal replacement therapy. AKI, Acute kidney injury; ICU, Intensive Care Unit; RRT, Renal Replacement Therapy