Comparison of renal replacement therapy and renal recovery before and during the COVID-19 pandemic- A single centre observational study

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Abstract

Background: To compare differences in indications, management, complications and outcomes of renal replacement therapy (RRT) in COVID-19 patients compared to non-COVID critically ill patients.

Methods: We conducted a retrospective observational single centre cohort study in UK. Patients with COVID-19 requiring RRT, compared to consecutive, non-COVID-19 ICU patients requiring RRT

Results: Of 154 COVID-19 patients, 47 (30.5%) received continuous venovenous haemofiltration (CVVHF), all of whom required mechanical ventilation and vasopressor support. The requirement for RRT was related to fluid balance rather than azotaemia. Compared to 36 non-COVID-19 patients, those with COVID-19 were younger with a lower serum creatinine on hospital admission, and lesser degrees of metabolic acidosis and lactataemia before initiation of RRT. In addition, the rate of haemofilter circuit clotting was higher and duration of RRT requirement was longer. However, despite lower CVVHF exchange rates with higher serum creatinine levels following RRT initiation in the COVID-19 patients, metabolic abnormalities were corrected. Hospital mortality was 60% among COVID-19 patients requiring RRT, compared to 67% in non-COVID patients (p=0.508), and renal recovery among survivors was similar.

Conclusion: The metabolic phenotype in COVID-19 patients requiring RRT differs from non-COVID-19 patients, although outcomes (mortality and renal recovery) are similar.

Introduction

Provision of renal replacement therapy (RRT) for patients with COVID-19 was challenging for both logistical and disease-related factors [1]. A significant proportion of COVID-19 patients developed acute kidney injury (AKI), many of whom require RRT [2]. In our institution, as with many others, shortages of continuous venovenous hemodiafiltration (CVVHDF) machines and replacement fluids necessitated reduced intensity of hemofiltration (exchange rates) to facilitate the greatly increased demand for RRT capacity. Patients with COVID-19 are at increased risk of thrombotic complications [3], creating challenges around optimizing the anticoagulation to preserve filter life. This was further compounded by the lack of citrate regional anticoagulation.

To assess the impact of these modifications, and any differences in thresholds for the initiation of RRT, and we drew comparison against consecutive non-COVID-19 critically ill patients in our intensive care unit requiring RRT over the previous year. We specifically addressed differences in initiation criteria for RRT, fluid balance and azotaemia with different clearance rates, incidence of hemofilter clotting, duration of RRT prior to renal recovery, hospital survival, and renal recovery.

Materials And Methods

We conducted a single-centre retrospective case control study of patients with COVID-19 requiring acute RRT on the intensive care unit at University College London Hospital between 1st March and 30th June 2020. Comparison was made against those receiving RRT in the pre-COVID period from January 2019 to February 2020. Our hospital lacks a renal dialysis unit so ICU admission is required for all patients with acute kidney injury needing RRT.

Data were extracted from electronic healthcare records on patient demographics, RRT parameters, anticoagulation, biochemistry and fluid balance on the day of RRT initiation, creatinine clearance rates, the incidence of filter clotting, duration of RRT, renal function on discharge from hospital, and hospital survival. Patients receiving chronic dialysis were excluded as our study sought to assess criteria for RRT initiation and renal recovery rates.

Details of the UCLH pre-COVID-19 protocol and shortage-driven modifications during COVID-19 are detailed in the Supplementary Appendix. Briefly, prior to COVID-19, the standard of care was citrate-based regional anticoagulation and initiation of CVVHDF at exchange rates of 1000 ml/hr for both hemofiltration and dialysis. During shortage periods, COVID-19 patients received continuous venovenous hemofiltration (CVVHF) initiated at an exchange rate of 1000 ml/hr. In cases where augmented small molecule clearance was required, 1000 ml/hr dialysis was subsequently added until desired biochemistry was achieved. Prophylactic anticoagulation using low molecular weight heparin (enoxaparin) was routinely increased in all COVID-19 patients from 40 mg once daily to 40 mg twice daily. Therapeutic doses were given to those with diagnosed venous, pulmonary or systemic arterial thromboembolism. During periods of citrate unavailability, therapeutic dose low molecular weight heparin (LMWH) was used to maintain filter patency.

As this was a retrospective observational study, we did not define any sample size. Anonymised data were used for analysis. No patients were missing the primary outcome or key confounders (details in Supplementary data). Continuous and categorical variables are reported as median (interquartile range) and n (%), respectively. For continuous variables, the Mann Whitney U test was used for comparison between groups. Categorical data were compared using the chi-squared test. Changes in biochemistry or fluid balance over time was assessed using 2-way ANOVA. Statistical analysis was performed, and graphs drawn using SPSS (Version 26.0) and Prism (GraphPad Software, Version 5.0d, San Diego, CA, USA).

Evaluation of novel observational data on the management of COVID-19 patients received ethical approval from London-Westminster Research Ethics Committee and the Health Research Authority (REC

ref 20/HRA/2505 and IRAS ID 284088). As data on routine RRT management are collected as part of routine service evaluation within our institution, specific permission was not required for data obtained from pre-COVID patients.

Results

Demographics

Of 154 patients admitted to our ICU with COVID-19 disease, 47 (30.5%) required RRT. Of these, 26 were transferred from other hospitals. Comparison was made against a contemporaneous cohort of consecutive non-COVID-19 critically ill patients who required RRT in ICU during the course of the preceding year. Of the 44 non-COVID-19 patients that required RRT, 8 had end-stage renal disease (ESRD) and were excluded, leaving 36 non-COVID-19 patients in the final analysis. Among non-COVID-19 patients, the primary aetiology of AKI included sepsis (47.2%), hypovolaemia (5.5%), post- major surgery (8.3%), post- cardiac arrest (8.3%) and other causes (30.6%) (**Supplementary Table 1**).

There were no significant between-group differences in gender, body mass index (BMI), time from hospital admission to ICU admission, and proportions of patients with hypertension and diabetes mellitus (**Table 1**). Non-COVID-19, patients were older, more likely to have chronic kidney disease (CKD), and had a higher serum creatinine on hospital admission. Censored for patients without CKD, the between-group difference in admission serum creatinine remained significant (**Table 1**).

A greater proportion of COVID-19 patients with required invasive mechanical ventilation (IMV) (100% vs 75%; $p<0.001$) and vasopressors (100% vs. 86%); $p=0.008$). Although time from hospital admission to requiring IMV was similar, the median time from IMV requirement to RRT requirement was a week longer in COVID-19 patients (**Table 1**).

RRT initiation, clearance, and discontinuation

No inter-group differences were seen in cumulative fluid balance, urine output in the preceding 24 hours, pH, potassium, serum creatinine or urea on initiation of RRT ($p>0.05$) (**Supplementary Table 2**). Non-COVID-19 patients had markedly higher values of PaO_2:FiO_2 ratio, arterial lactate and base deficit, and a lower serum bicarbonate (**Figure 1, Supplementary Table 2**).

Initiation of RRT achieved significant reductions in daily fluid balance in both groups, with COVID-19 patients achieving a greater net negative fluid balance (**Figure 2; Supplementary Table 3**). However, despite the reduction in fluid balance, there was no improvement in PaO_2:FiO_2 ratio in either group ($p=0.797$), with a persistently lower PaO_2:FiO_2 ratio in COVID-19 patients ($p<0.001$). The degree of metabolic acidosis remained significantly less severe in COVID-19 patients despite a lower CVVHF exchange rate, and serum creatinine values remaining higher. The more profound degree of overall acidosis (arterial pH) in COVID-19 patients was related to a respiratory acidosis and therefore remained unchanged following initiation of RRT.

Anticoagulation and thrombosis

The overall incidences of filter clotting and blood transfusion requirements were higher in COVID-19 patients (**Supplementary Table 4**). All non-COVID-19 patients received citrate regional anticoagulation.

Twenty-seven of the 47 (57%) COVID-19 patients requiring acute RRT were diagnosed with a venous thromboembolic event (VTE), all of whom received therapeutic low molecular weight heparin (LMWH). In addition, seven patients received regional citrate anticoagulation. Of the 20 patients without any evidence of VTE during admission, 17 were initiated on citrate anticoagulation with prophylactic LMWH while 3 patients were initiated on RRT with therapeutic anticoagulation with LMWH without citrate. Nineteen patients switched from regional citrate anticoagulation to systemic LMWH anticoagulation or *vice versa* depending on citrate availability. The 20 COVID-19 patients without diagnosed VTE had a similar incidence of filter clotting compared to the 27 patients with VTE. There was also no difference in the incidence of circuit clotting between days on citrate and days on LMWH.

Clinical outcomes

Hospital mortality was similar between patients with and without COVID-19 (60% vs. 68%; $p=0.508$) (**Table 2**). Among survivors, the duration of RRT, IMV, ICU stay and time from RRT cessation to hospital discharge was greater among COVID-19 patients. On hospital discharge, serum creatinine was significantly lower among patients with COVID-19 (**Figure 3**), excluding one patient with COVID-19 who was referred for ongoing RRT. Censored for patients without CKD, hospital discharge serum creatinine was comparable to patients without COVID (**Table 2**).

Discussion

Data on acute RRT during the COVID-19 pandemic have not been described in detail, nor a comparison made against a non-COVID cohort. The cohort of COVID-19 patients in our center were comparable in age and gender to the published literature [4]. Compared to patients without COVID-19, patients with COVID-19 were younger, had a lower serum creatinine on hospital admission, and were less likely to have CKD. As respiratory failure is the primary manifestation of COVID-19, it is unsurprising that all COVID-19 requiring RRT also required IMV. All however required vasopressor support which, in view of the normal lactate level in the majority of patients, is more likely to reflect hypotension due to a combination of hemodynamic consequences related to sedation use and high airway pressures rather than the metabolic effects of sepsis.

The metabolic phenotype in COVID-19-associated AKI differs from that seen in non-COVID patients in other respects. Firstly, the much later requirement for RRT in COVID-19 patients was not related to any significant delay in initiation as urea, creatinine, fluid balance and urine output values were similar to non-COVID-19 patients despite a far less severe metabolic acidosis. In the COVID-19 patients RRT was primarily initiated for ultrafiltration to achieve a neutral fluid balance with the aim of improving oxygenation[5]. However, our data show no effect on P:F ratio over the first 48 hours, despite active fluid removal. The much earlier use of RRT in non-COVID-19 patients who were more acidotic also implies a much higher degree of catabolism in these patients.

Severe COVID-19 disease is associated with endothelial activation and a hyperinflammatory, pro-thrombotic state [6, 7]. Despite patients with COVID-19 receiving augmented prophylactic dose LMWH with regional citrate anticoagulation, the incidence of filter circuit clotting was higher than in patients without COVID-19 on regional citrate anticoagulation. On average, one in 11 CVVHDF circuits in COVID-19 patients clotted each day. There was an associated increase in RBC transfusion requirements among COVID-19 patients requiring one unit every eight days. No differences were found however in the rate of filter clotting between the use of regional citrate anticoagulation or therapeutic systemic anticoagulation with LMWH.

The duration of RRT was longer compared to non-COVID-19 AKI, and IMV was often required after renal function recovered. Despite a greater proportion of COVID-19 patients requiring three organ support (respiratory, renal and cardiovascular), survival rates were similar to non-COVID-19 patients. Rates of mortality of COVID-19 patients receiving both IMV and RRT are comparable to other published data [8]. The aetiology of AKI in COVID-19 is multifactorial including haemodynamic compromise, inflammatory

mediators, and direct viral infection of glomerular and tubular cells [9, 10]. However, renal function recovered in almost all survivors by hospital discharge.

As with all retrospective analyses, we acknowledge that findings are associative. This is a single centre study with relatively limited numbers. Our clinical criteria for ICU admission and RRT may differ from other centres, potentially limiting generalisability. However, our patient demographics are consistent with published COVID-19 data. Baseline renal function was unavailable for some patients so the presence of CKD may be under-estimated. The PaO_2: FiO_2 ratio does not reflect details on mechanical ventilator settings, although is unlikely to alter the conclusion given the large difference between non-COVID and COVID-19 patients. Furthermore, data on sequential fluid balance and serum creatinine following initiation of RRT do not factor in survival bias, where some patients may not have survived 3 days following RRT initiation (details in supplementary data).

In summary, a third of critically ill patients with COVID-19 on the UCLH ICU required acute RRT. Compared to patients without COVID-19, they were younger, had a lower serum creatinine on hospital admission, and were less likely to have CKD. RRT was initiated much later following ICU admission in COVID-19 patients, primarily for fluid balance rather than acidaemia or hyperkalaemia. COVID-19 patients were successfully managed with reduced CVVHDF exchange rates. Duration of RRT requirement is longer compared to non-COVID-19 patients despite lower serum creatinine on hospital admission and lower rates of CKD in COVID-19 patients. Requirement for ongoing IMV precludes intermittent RRT in a nephrology acute dialysis unit. Hospital mortality was equally high in both COVID-19 and non-COVID-19 patients, and renal recovery among survivors was comparable.

Declarations

Acknowledgements: UCLH ICU team

Funding: None

Conflicts of Interest: None

Ethics approval: As data on routine RRT management are collected as part of routine service evaluation within our institution, specific permission was not required for data obtained from pre-COVID patients. Evaluation of novel observational data on the management of COVID-19 patients received ethical approval from London-Westminster Research Ethics Committee and the Health Research Authority (REC ref 20/HRA/2505 and IRAS ID 284088).

Availability of data and material: Available upon reasonable request

Author contribution: Study design (NA), data collection (RR, IT), statistics (NA), drafting manuscript (NA), finalising manuscript (NA, CL, NM, MS).

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Tables

	Non-COVID-19	COVID-19	p-value
	N=36	N=47	
Age (years)	68 (54 – 73)	61 (52 – 66)	0.016
Gender (male)	23 (64%)	34 (72%)	0.411
Body mass index (kg/m^2)	29 (22 – 33)	26 (23 – 29)	0.214
Hospital admission creatinine (mmol/L)	167 (108-292)	102 (79 – 173)	0.014
Hospital admission creatinine without chronic kidney disease (mmol/L)	152 (106-290))	102 (79-173)	0.049
Chronic kidney disease	7 (19%)	1 (2%)	0.008
Diabetes mellitus	7 (19%)	11 (23%)	0.664
Hypertension	20 (56%)	22 (47%)	0.430
Hospital admission to ICU admission (days)	1.0 (0.0-2.5)	1.0 (0.0-2.0)	0.322
Vasopressor/ Inotrope use	31 (86%)	47 (100%)	0.008
Invasive mechanical ventilation (IMV)	27 (75%)	47 (100%)	<0.001
Hospital admission to IMV (days)	1 (0-3)	3 (1-6)	0.065
Initiation of IMV to RRT initiation (days)	1.0 (0.0-2.0)	8.0 (2.0-17.0)	<0.001
Hospital admission to RRT initiation (days)	2.0 (1.0-8.0)	13.0 (7.0-18.0)	0.006

Table 1: Demographics and organ support requirements of COVID-19 and non-COVID-19 patients requiring RRT on ICU. (IMV: invasive mechanical ventilation; RRT: renal replacement therapy)

	Non-COVID-19	COVID-19	p-value
Survival to hospital discharge	12 (33%)	19 (40%)	0.508
Cessation of RRT to hospital discharge: survivors (days)	12 (6 – 26)	24 (7-29)	0.005
Creatinine on hospital discharge: survivors (mmol/L)	156 (94 – 342)	74 (56 – 99)	0.004
Creatinine on hospital discharge: survivors *without CKD* (mmol/L)	113 (69-222) (n=10)	77 (59-119) (n=20)	0.231
IMV duration: all patients (days)	5 (1- 11)	23 (10 -39)	<0.001
RRT dependence: survivors (days)	4.5 (2.5 – 9.5)	11.5 (8.0-18.0)	0.009
RRT dependence: all patients (days)	2.5 (1.0-8.0)	7.0 (3.0-16.0)	<0.001
IMV cessation to RRT cessation: survivors (days)	0 (-1 – 2.5)	-11 (-21 - 1)	0.042
ICU length of stay: survivors	10 (7-20)	45 (34 – 65)	<0.001
ICU length of stay: all patients	9 (3 – 20)	28 (12 – 44)	0.052

Table 2: Clinical outcomes. (ICU: Intensive care unit; IMV: invasive mechanical ventilation; RRT: renal replacement therapy; CKD: chronic kidney disease)

Figures

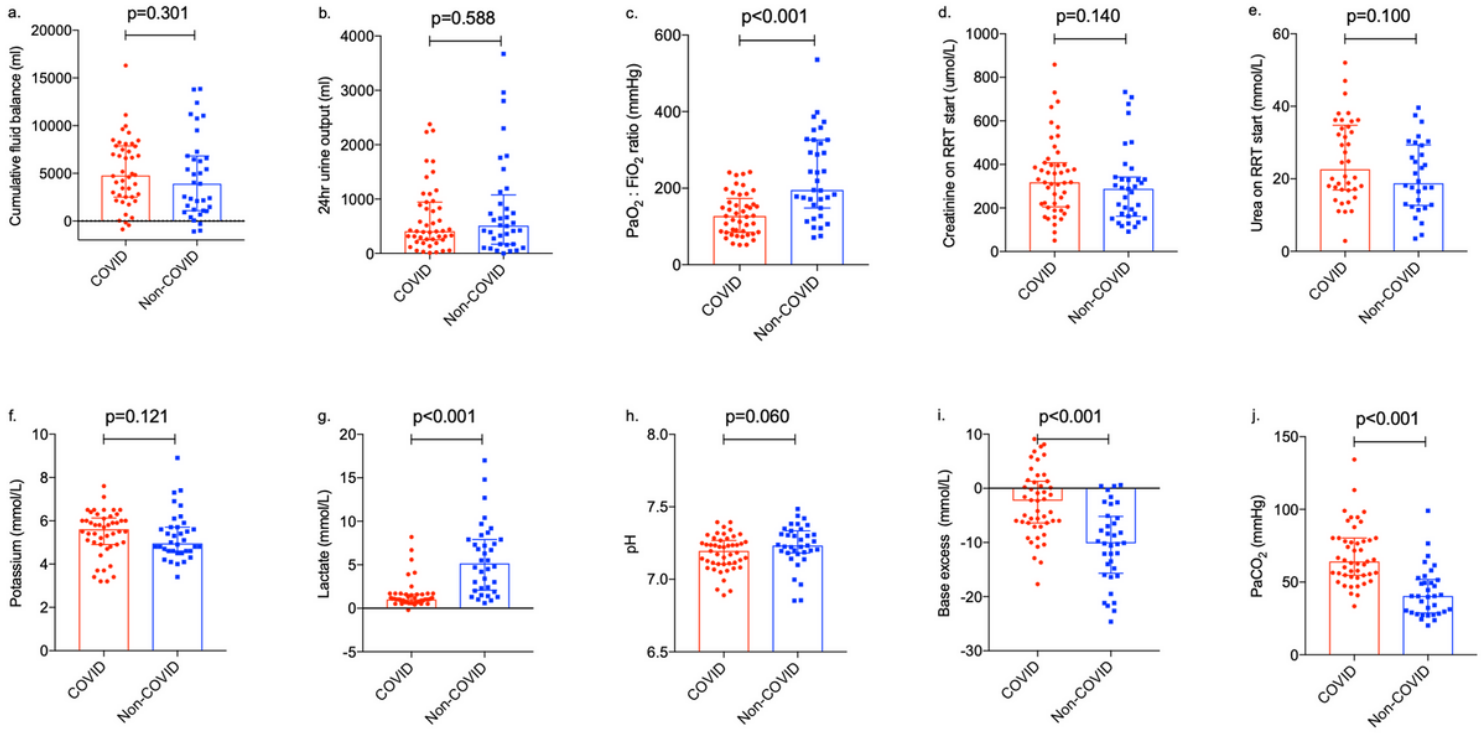

Figure 1

Clinical, biochemical, and gas exchange parameters on initiation of RRT. (a). Cumulative fluid balance and (b). urine output in the preceding 24hrs is similar between COVID-19 and non-COVID-19 patients. (c). Patients with COVID-19 are significantly more hypoxaemic on initiation of RRT. Biochemistry including (d). serum creatinine, (e). urea, and (f). potassium is similar between COVID-19 and non-COVID-19 patients. Non-COVID-19 patients have (g). significantly higher arterial lactate although (h). pH is similar to patients with COVID-19. (i). Base excess is more negative among non-COVID-19 patients whereas (j). arterial tension of carbon dioxide is higher among COVID-19 patients compared to non-COVID-19 patients. Data represent median values and interquartile ranges.

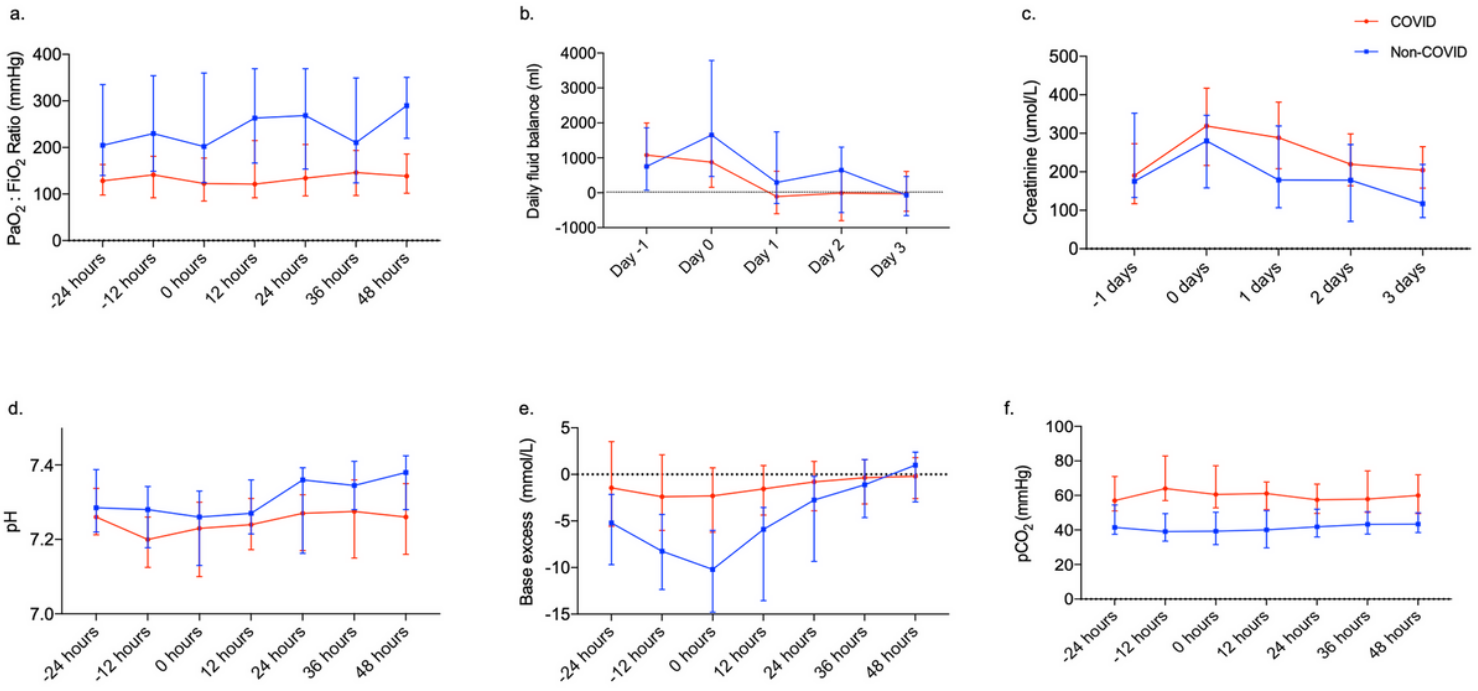

Figure 2

Changes in gas exchange and metabolic parameters following initiation of renal replacement therapy in mechanically ventilated patients. (a-b). Initiation of RRT achieved a significant reduction in daily fluid balance, although this did not result in an improvement in PaO2: FiO2 ratio. (c). Serum creatinine remained higher in the COVID-19 patients. (d-i). Patients with COVID-19 had milder metabolic acidosis compared to non-COVID patients which was corrected despite a lower CVVHF exchange rate. The greater acidosis in COVID-19 patients was secondary to a higher PaCO2. Data represent median values and interquartile ranges.

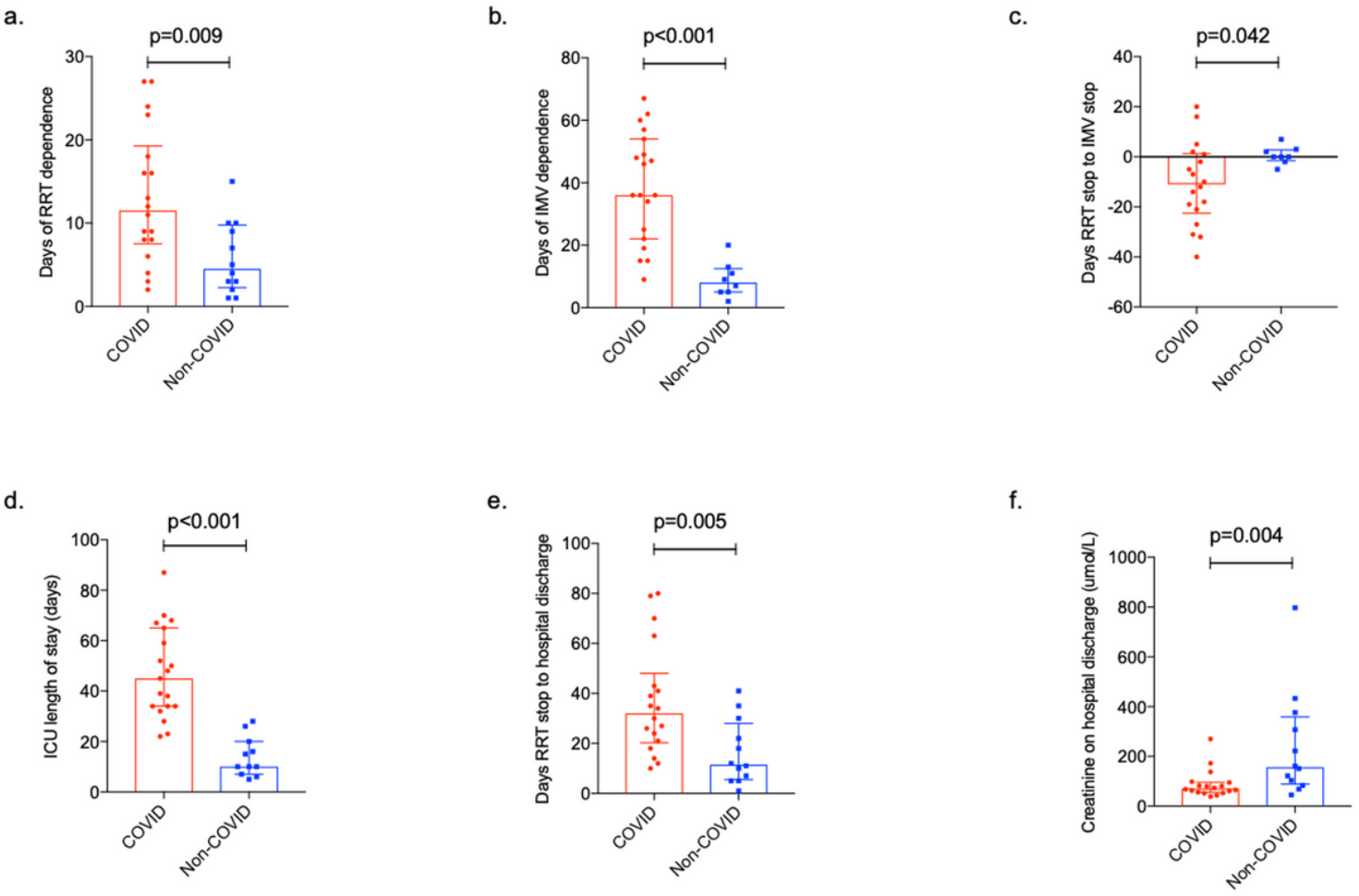

Figure 3

Clinical outcomes among survivors. Duration of (a). RRT dependence and (b). IMV dependence is significantly greater in COVID-19 survivors compared to non-COVID-19 survivors. (c). Among COVID-19 survivors, RRT discontinuation occurred much earlier than IMV discontinuation. (d). ICU length of stay and (e). time from RRT cessation to hospital discharge is longer in COVID-19 survivors. (f). Creatinine on hospital discharge is significantly lower in COVID-19 survivors compared to non-COVID-19 survivors. Data represent median values and interquartile ranges. (RRT: Renal replacement therapy; IMV: invasive mechanical ventilation; ICU: intensive care unit)

Supplementary Files

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- Supplementarydata.docx