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Original Article

Renal impairment and its impact on clinical outcomes in patients who are critically ill with COVID-19: a multicentre observational study

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Summary

Renal impairment is common in patients who are critically ill with coronavirus disease-19 (COVID-19). We examined the association between acute and chronic kidney disease with clinical outcomes in 372 patients with coronavirus disease-19 admitted to four regional intensive care units between 10 March 2020 and 31 July 2020. A total of 216 (58%) patients presented with COVID-19 and renal impairment. Acute kidney injury and/or chronic kidney disease was associated with greater in-hospital mortality compared with patients with preserved renal function (107/216 patients (50%) (95%CI 44–57) vs. 32/156 (21%) (95%CI 15–28), respectively; $p < 0.001$, relative risk 2.4 (95%CI 1.7–3.4)). Mortality was greatest in patients with renal transplants (6/7 patients (86%) (95%CI 47–100)). Mortality rates increased in patients with worsening renal injury according to the Kidney Disease: Improving Global Outcomes classification: stage 0 mortality 33/157 patients (21%) (95%CI 15–28) vs. stages 1–3 mortality 91/186 patients (49%) (95%CI 42–56); $p < 0.001$, relative risk 2.3 (95%CI 1.7–3.3). Survivors were less likely to require renal replacement therapy compared with non-survivors (57/233 patients (24%) vs. 64/139 patients (46%), respectively; $p < 0.001$, relative risk 1.9 (95%CI 1.4–2.5)). One-fifth of survivors who required renal replacement therapy acutely in intensive care continued to require renal support following discharge. Our data demonstrate that renal impairment in patients admitted to intensive care with COVID-19 is common and is associated with a high mortality and requirement for on-going renal support after discharge from critical care. Our findings have important implications for future pandemic planning in this patient cohort.

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Introduction

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a public health emergency of international concern with high levels of community transmission and a high mortality rate in high-risk groups [1]. The care of patients with COVID-19 has

put a significant strain on intensive care unit (ICU) resources worldwide. Reported mortality rates have varied from 40 to 50% and thus remain significant [2, 3].

Patients who are critically ill with COVID-19 often require respiratory support secondary to acute respiratory distress syndrome (ARDS) [4]. However, a large proportion of patients with COVID-19 appear to also manifest extra-pulmonary sequelae involving numerous organ systems [5]. The incidence of acute kidney injury (AKI) in patients infected with COVID-19 is between 3 and 6%, rising to 15–58% in those patients who are critically ill. Non-survivors have an incidence of AKI that is considerably higher than survivors (53% vs. 1%), suggesting that the onset of AKI correlates not only with disease severity but may also have prognostic significance [6]. Furthermore, in those patients who require renal replacement therapy (RRT), the impact on resource utilisation is considerable, especially in a pandemic situation where resources may have to be rationed [7, 8].

Patients with chronic kidney disease (CKD) account for approximately 10% of ICU admissions [9, 10]. However, in the current COVID-19 pandemic, outcomes for patients who are critically ill and have CKD, end-stage renal failure (ESRF) or have undergone a renal transplant, are often not included in analyses [11–13]; even when these patient cohorts are analysed, the number of patients included are small [14–18]. In addition, although the estimated rate of RRT following AKI is approximately 5% in ICU [19], there is a paucity of data on RRT requirements for those patients who survive an ICU admission for COVID-19 involving AKI [11]. We aimed to characterise the clinical outcomes of patients who are critically ill with COVID-19 and had AKI, pre-existing CKD and/or ESRF.

Methods

This report was prepared using the strengthening of observational studies in epidemiology (STROBE) guidelines [20]. Ethical approval was not required as this study was carried out as a service evaluation within the NHS and recorded under the auspices of the clinical audit office at Imperial College Healthcare NHS Trust and University Hospitals Birmingham NHS Foundation Trust.

We retrospectively evaluated all adult patients (aged ≥ 18 years) admitted to ICU with a confirmed diagnosis of COVID-19 pneumonia (made using real-time polymerase chain reaction assay), at three teaching hospitals in London (Hammersmith Hospital, Charing Cross Hospital and St Mary's Hospital, all part of Imperial College Healthcare NHS Trust) and one hospital in Birmingham (Queen Elizabeth Hospital, part of University Hospitals Birmingham NHS Foundation Trust) from 10 March to 23 July 2020.

Patients were categorised into five groups: those who had no kidney injury; those who developed new onset AKI; those with pre-existing CKD; those with ESRF; and those who underwent a renal transplant. Kidney injury was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (see online Supporting Information, Appendix S1). Baseline serum creatinine was defined as the latest serum creatinine value before presentation (if known). Patients with CKD were identified as those who had a formal diagnosis of CKD documented in their medical notes before admission.

The primary outcome measure was in-hospital mortality. Secondary outcome measures included: change in mean creatinine (baseline to peak); and the need for RRT during ICU stay and after discharge from ICU. The following additional data were also recorded: baseline/community renal function; patient baseline characteristics; ICU clinical data including hourly urine output; acute physiology and chronic health evaluation (APACHE 2) score; ventilation requirements; laboratory tests (haematological and biochemical); and mode(s) of RRT.

A sample size was not calculated as this was an observational study and all eligible patients were included. Shapiro–Wilk normality tests were carried out and comparisons between groups were performed using ANOVA (with Sidak's correction for multiple comparison) for parametric data. Categorical data analyses were made using chi-square test with Fisher's correction. All data were analysed on GraphPad Prism (v8.00; GraphPad Software, San Diego, CA, USA). A value of $p < 0.05$ was defined as the minimal threshold for statistical significance.

Results

A total of 372 ICU patients were included. Of those, 156 patients (42%) had no renal impairment during their ICU stay, 168 patients (45%) developed AKI and 48 patients (13%) had pre-existing kidney impairment (Fig. 1). Patient baseline characteristics are shown in Table 1. The study cohort had a median (IQR [range]) age of 59 (51–65 [21–89]) years with a male predominance (269 men (72%)) and the majority of patients were from a Black, Asian and minority ethnic (BAME) background (281 patients (76%)). The median (IQR [range]) APACHE-2 score was 15 (11–20 [2–66]). In total, 337 patients (91%) required mechanical ventilation.

Overall, 139 patients (37%) died. Patients with AKI and/or CKD had a greater in-hospital mortality compared with patients with preserved renal function: 107/216 patients (50%)

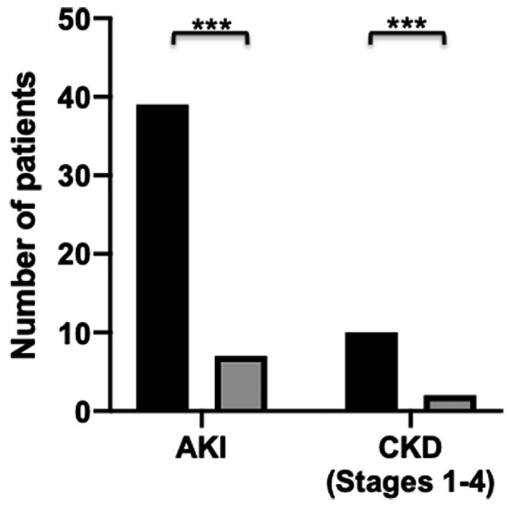

Figure 1 Number of patients requiring long-term renal replacement therapy after discharge from ICU ■. Renal replacement therapy in ICU and renal replacement therapy post-ICU ■. ***$p < 0.001$. AKI, acute kidney injury; CKD, chronic kidney disease.

(95%CI 43–56)) vs. 32/156 patients (21%) (95%CI 15–28)), respectively; $p < 0.001$; relative risk (RR) (95%CI) 2.4 (1.7–3.4).

Broadly similar mortality rates were seen in patients with new onset kidney injury (81/168 patients (48%) (95%CI 41–56)), pre-existing CKD (stages 1–4) (11/22 patients (50%) (95%CI 31–69)) and ESRF (9/19 patients (47%) (95%CI 27–68)). Mortality was highest in patients who had undergone a renal transplant previously (6/7 patients (86%) (95%CI 47–100) (Table 1). In patients with AKI or CKD (stages 1–4), higher KDIGO stages were associated with an increased need for RRT and a greater mortality risk (Table 2). Mortality in patients with stage 0 (i.e. preserved baseline renal function) 33/157 patients (21%) (95%CI 15–28%)) compared with stages 1–3 91/186 patients (49%) (95%CI 42–56)); $p < 0.0001$; RR 2.3 (95%CI 1.7–3.3).

Peak serum creatinine values were raised from baseline in all patients with any form of kidney impairment demonstrating deterioration of kidney function during their illness. The largest relative increase in serum creatinine occurred in patients with new onset AKI (Table 1).

In the cohort of 216 patients with any form of kidney impairment, 121 (56%) patients required RRT (Table 1). The commonest mode of RRT was haemodiafiltration alone, followed by intermittent haemodialysis alone. A lower proportion of patients underwent a combination of haemodiafiltration, intermittent haemodialysis or acute peritoneal dialysis alone (for surge-related operational reasons). Of the 48 survivors who required RRT acutely during their critical care stay (39 patients with AKI and 9 patients with CKD), nine (19%) patients required RRT after discharge from the ICU during the follow-up period to hospital discharge (Fig. 1). Overall, 24% (57/233 patients) of survivors needed RRT at some point during their critical illness, compared with 46% (64/139 patients) of non-survivors ($p < 0.001$; RR 1.9 (1.4–2.5)). Notably, however, once RRT had been established, there was no difference between survivors and non-survivors in patients with new-onset AKI (39/82 patients (48%) vs. 43/82 patients (52%)) and those patients with pre-existing CKD stages 1–4 (8/17 (47%) vs. 9/17 patients (53%)).

Discussion

In this multicentre retrospective study, we investigated the outcomes of patients who were critically ill with COVID-19 and had pre-existing renal impairment or new kidney injury. We made a number of important findings: first, patients who are critically ill with COVID-19 and have any form of renal impairment experience high mortality rates; second, mortality in patients with new AKI and pre-existing CKD is comparable, with the exception of those patients with renal transplants who are an extremely vulnerable group; third, mortality is increased in patients with worsening KDIGO stages of kidney injury; fourth, a significant proportion of patients who survive need long-term RRT following discharge from ICU; and finally, survivors are less likely to require RRT during their ICU admission. To the best of our knowledge, this is the first comprehensive analysis of outcomes in patients who are critically unwell with COVID-19 and have renal impairment, particularly those patients with pre-existing CKD [21].

The incidence of AKI in patients with non-COVID-19 ARDS is reported as approximately 44% and has a mortality of 42% [22]. However, our data demonstrate that patients are more at risk of developing renal impairment with COVID-19 infection which translates to a higher mortality rate. The high mortality rates observed in our study cohort of patients with AKI and COVID-19 infection is similar to other studies [23]. However, unlike other reports, we also investigated patients with pre-existing renal pathologies and included those patients with a previous, viable renal transplant and those with CKD. The mortality rate of recipients of renal transplants is markedly higher than the other groups and these patients are, therefore, an extremely vulnerable group. There are several possible reasons for this such as the pre-existing immunosuppressed state and associated comorbidities of this patient sub-group [24].

Surprisingly, mortality rates of patients with CKD stages 1–4, new kidney impairment and ESRF were comparable, although these were more than double the mortality rates seen in patients without renal impairment. While there may

Table 1 Characteristics of 372 patients admitted to four regional intensive care units with COVID-19 stratified into five groups according to the type of observed renal impairment. Values are median (IQR [range]), number (proportion) or mean (SD).

	No renal impairment (n = 156)	New AKI (n = 168)	Pre-existing CKD (stage 1–4) (n = 22)	ESRF (n = 19)	Renal transplant (n = 7)
Age; years	54 (46–63 [21–89])	60 (52–66 [24–82])	60 (54–66 [32–78])	60 (57–68 [29–88])	60 (55–65 [48–69])
Sex; male	102 (65%)	134 (80%)	18 (82%)	9 (47%)	6 (86%)
Ethnicity, n (%)					
White	37 (24%)	46 (27%)	6 (27%)	3 (16%)	
Asian	31 (20%)	38 (23%)	8 (36%)	5 (26%)	4 (57%)
Black	16 (10%)	19 (11%)	3 (14%)	9 (47%)	1 (14%)
Other	72 (46%)	65 (39%)	5 (23%)	2 (11%)	2 (29%)
APACHE 2 score	12 (10–15 [2–56])	16 (13–20 [4–63])	22 (16–28 [10–63])	25 (23–43[17–66])	34 (32–42 [19–63])
Serum creatinine; $\mu mol.l^{-1}$					
Baseline	76 (18)	77 (18)	221 (217)	643 (455)	244 (123)
Peak	91 (38)	324 (210)*	466 (264)*	1163 (532)*	479 (182)†
No renal replacement therapy	156 (100%)	86 (51%)	7 (32%)	–	2 (29%)
Mode of renal replacement therapy					
Haemodiafiltration	n/a	75 (45%)	13 (59%)	11 (58%)	5 (71%)
Intermittent haemodialysis	n/a	3 (2%)	–	6 (32%)	–
Haemodiafiltration/ intermittent haemodialysis	n/a	2 (1%)	2 (9%)	2 (11%)	–
Haemodiafiltration/ peritoneal dialysis	n/a	1 (1%)	–	–	–
Peritoneal dialysis	n/a	1 (0.6%)	–	–	–
In-hospital mortality (95%CI)	32 (21% (15–28))	81 (48% (41–56))	11 (50%) (31–69))	9 (47%) (27–68))	6 (86%) (47–100))

AKI, acute kidney injury; CKD, chronic kidney disease; ESRF, end-stage renal failure; APACHE, acute physiology and chronic health evaluation.
*$p < 0.001$ compared with baseline.
†$p < 0.05$ compared with baseline.

have been selection bias in patients admitted to ICU with a history of renal disease, these encouraging results have potential connotations for future surges, suggesting that ICU admission may be entirely appropriate for patients who are critically ill with COVID-19 and have CKD (including ESRF). We also showed that severity of kidney injury was associated with higher mortality rates. These data highlight that clinicians should aim to recognise and proactively manage worsening kidney injury in patients with COVID-19 before progression to KDIGO stage 2 and beyond, where mortality increases significantly.

Albeit not specific to COVID-19-associated AKI, management strategies include: avoidance of nephrotoxic drugs; lung-protective ventilation to prevent the adverse haemodynamic effects that can be associated with mechanical ventilation; and maintenance of euvolaemia to prevent AKI from either hypovolaemia or fluid overload and resultant congestion [25]. A significant proportion of patients with KDIGO stage-3 AKI required RRT and we were able to demonstrate that modes other than continuous RRT by haemodiafiltration, such as intermittent haemodialysis and acute peritoneal dialysis, are possible.

While these data clearly demonstrate that COVID-19 infection has an effect on the renal system, the pathophysiology of this is not well understood due to the lack of renal biopsies in patients who are critically ill with COVID-19. Several post-mortem studies have postulated that the renal injury is due to direct infection, with the virus causing an endotheliitis similar to its postulated effect in the lung [26–28], although concerns have been raised

Table 2 Requirement for renal replacement therapy (RRT) stratified for different Kidney Diseases: Improving Global Outcomes (KDIGO) stages in 369 patients who were critically ill with COVID-19. The various forms of renal replacement therapy commenced in 212 patients with associated mortality rates are also shown. Values are number (proportion).

KDIGO stage	Frequency	Mortality	Requiring RRT
0	157 (43%)	33 (21%)	–
1	43 (12%)	15 (35%)	10 (23%)
2	38 (10%)	23 (61%)	11 (29%)
3	105 (28%)	53 (50%)	75 (71%)
End-stage renal failure	19 (5%)	9 (47%)	19 (100%)
Renal transplant	7 (2%)	6 (86%)	5 (71%)
Mode of renal replacement therapy			
Haemodiafiltration	103 (49%)	59 (57%)	
Intermittent haemodialysis	9 (4%)	4 (44%)	
Haemodiafiltration and intermittent haemodialysis	6 (3%)	1 (17%)	
Haemodiafiltration and peritoneal dialysis	1 (0.5%)	–	
Peritoneal dialysis	1 (0.5%)	–	

subsequently about the validity of these data [29]. Recent data also suggest the possibility of lung-to-kidney cross talk, with an initial injury to the lungs followed by kidney failure several days later mediated by inflammatory particles such as cytokines (e.g. tissue necrosis factor) or extracellular vesicles [30–32]. Furthermore, drug toxicity from excessive diuresis, antimicrobial therapy or contrast exposure may also play a role. There may also be other contributing factors such as hypotension, volume depletion, hypercoagulability and cardiac dysfunction [30]. Therefore, it could be postulated that the kidneys are likely to reflect the severity of COVID-19 pneumonitis, with the renal injuries observed due to multimodal pathologies rather than direct viral injury; however, studies involving renal biopsies would be needed to evaluate this. Further urgent mechanistic work is required to greater understand the pathophysiology of kidney injury and failure in patients with COVID-19, which may translate to the development of novel therapies and allow recognition of those patients at particular risk.

We found that 19% of survivors who had received RRT acutely required dialysis on discharge from the ICU. Although our follow-up period was not long enough to determine the long-term risks of developing CKD or ESRF in patients with new kidney impairment associated with COVID-19, it potentially indicates a higher risk for long-term RRT requirement, compared with unselected critical care cohorts. This would have significant healthcare implications if these results were replicated in a study with a longer period of follow-up [24]. Ostensibly, the short follow-up period negates any direct comparison with previously published data on this point save for two points of discussion. First, it is possible that some of our patients would continue to exhibit further recovery of renal function after hospital discharge negating the need for ongoing RRT. Second, if indeed patients with COVID-19 have an increased risk to long-term RRT, then the question remains whether this is due to the underlying pathology or a consequence of practice (such as timing of initiation of RRT) especially in view of recently published evidence [21]. Nevertheless, irrespective of the debate around the long-term requirement for RRT, our data reassuringly showed similar mortality rates in patients who needed to commence acute RRT on ICU and had either AKI or CKD. These findings have potential implications for the management of CKD and ESRF patients in any future surge.

Although this study included a relatively large number of patients with COVID-19 and renal impairment, it has several limitations. First, our cohort of patients included a larger proportion of non-white patients (76% vs. 33%) and patients with pre-existing CKD (13% vs. 8%) compared with the Intensive Care National Audit and Research Centre (ICNARC) database and therefore may not be translatable to the rest of the UK population [33]. Second, this is a retrospective observational study without any non-COVID-19 matched controls or controls with COVID-19 not admitted to ICU. Third, the aetiology of AKI was not determined by renal biopsy, precluding direct evaluation of the renal effects of COVID-19 or any inflammatory response implicated in its pathology. Additionally, while we compared mortality between AKI, CKD stages 1–4 and ESRF, there was likely to be some selection bias in those patients admitted to ICU, which may have had a positive effect on our mortality outcomes. Finally, confounding variables were not controlled for

between groups of patients examined in this study (as it was not powered to allow for regression analysis) introducing the possibility of other factors beyond renal function impacting on outcomes.

In conclusion, there was a high prevalence of AKI in patients who were critically ill with COVID-19. However, important differences exist between stages of acute and CKD in how they affect mortality in patients with COVID-19, and patients with renal transplantation are an extremely vulnerable group. In view of this, attention needs to be paid to patients with COVID-19 with any form of renal impairment and every effort made to prevent progression of renal injury in order to reduce mortality. Once the need for acute RRT has been established, there was no difference in mortality rates for patients with AKI compared with those with CKD. Furthermore, the overall mortality rates for patients with AKI, CKD and ESRF are broadly similar, which potentially has implications for prognostication and resource allocation.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Diagnostic criteria for the differing Kidney Disease: Improving Global Outcomes (KDIGO) stages.