The changing nature of COVID-19 associated AKI: Where are we now?

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Since the emergence of the Sars-CoV-2 (COVID-19) pandemic a huge amount of research and data collection has allowed better understanding of the epidemiology of the disease. Although the virus predominantly affects the respiratory system it is clear that other organ systems can also be affected, with acute kidney injury (AKI) one of the most common complications [1, 2]. Whilst specific forms of renal disease (e.g. collapsing glomerulopathies) have been described, the majority of cases reflect the effects of an acute systemic inflammatory illness on the kidney [3, 4]. Risk factors for developing COVID-19 associated AKI have been well-described and include gender, ethnicity, requirement for invasive ventilation and pre-existing long-term conditions, for example diabetes mellitus or chronic kidney disease (CKD) [5]. The presence of AKI is also strongly associated with increased short-term mortality [5]. One of the most striking observations is that the incidence of COVID-19 associated AKI has reduced over time, with progressively lower rates of kidney replacement therapy (KRT) observed in the second and third waves as compared to the beginning of the pandemic [6]. There are a number of putative reasons for this, including improved recognition of AKI coupled to guidelines on care (e.g. from National Institute for Health and Care Excellence [7]), a move away from restrictive fluid strategies, introduction of effective therapies and vaccination for COVID-19, and reduced rates of invasive mechanical ventilation. However, the relative contribution of different factors has not been rigorously studied.

In this issue of *NDT,* Sullivan et al. report results from a large UK-wide cohort study that focusses on this question. Analyses were performed using data collected within the International Severe Acute Respiratory Infection Consortium Coronavirus Clinical Characterisation Consortium (ISARIC4C), an example of a research structure in

place prior to the current pandemic, which was ready to respond to a major infectious disease outbreak. It was therefore possible to collect prospective data from the time of the first reported cases in the UK and do so at scale, involving 254 hospitals and assembling a cohort of 114,131 patients who met the inclusion criteria for this analysis. This study used data collected between January 17th 2020 and December 5th 2020, capturing the first and part of the second UK waves of the pandemic. As well as studying associations and outcomes of AKI, the analyses also sought to identify factors that were associated with changes in the rates of AKI over time. The study was not designed to report longer term outcomes or examine the rates of chronic kidney disease after AKI. Two groups were defined: i) patients who needed acute KRT (n=85,687); and ii) 'biochemical AKI' representing patients with AKI identified based on changes in serum creatinine (using the NHS AKI detection algorithm and the KDIGO AKI criteria) who did not receive KRT (n=41,294). In the latter group, the majority of AKI was stage 1 (65.9%) and 55% was present at time of admission to hospital. AKI even in its mildest form was associated with an increased mortality, 40% of all AKI patients died during the 28-day follow-up, and there was a step-wise increase in the risk of death with each increase in AKI stage. Confirming prior findings, risk factors for both AKI and KRT included obesity, pre-existing CKD, male gender, and black race, with those of Asian ethnicity also at increased risk in combination with co-morbidities, especially CKD.

The study also described a clear fall in the rates of KRT and biochemical AKI over the data collection period. Rates of both were highest between Feb-April 2020 then subsequently fell, with the relative fall in rates of KRT appearing greater than that seen in biochemical AKI. Whilst rates of KRT were <1% in December 2020 versus

4% at peak, rates of AKI had fallen from 33.8% but remained at >20%. This observation, along with the significant association of AKI with adverse outcomes, reinforces the ongoing importance of recognising and responding to AKI in hospitalised patients with COVID-19.

But what underlies the temporal changes? The current study was not designed to examine processes of care, and the marginal reduction in 4C mortality score over time suggests at most a small effect from reducing illness severity or fewer co-morbidities. The authors therefore examined associations between treatment with dexamethasone and remdesivir on rates of KRT and biochemical AKI, but found either no relationship, or even a paradoxical association of greater dexamethasone use in those receiving KRT. This is a major point of discussion, as these results are in conflict with those from the RECOVERY trial that demonstrated a significant reduction in KRT in the dexamethasone arm [8], and with other observational studies in which steroids are associated with lower rates of progression of AKI to higher stages [9]. Although Sullivan et al used propensity matching to reduce differences in participant characteristics in comparisons between those who did and did not receive dexamethasone, the risk of residual confounding remains. This may explain the positive association of dexamethasone with increased rates of KRT, if for example more severely unwell patients (who were not identifiable from the dataset) were also more likely to receive dexamethasone. The analyses on medications included data only from June 2020 onwards, whilst the largest changes in the rates of KRT had already occurred in the period up to May 2020. This may have made it more difficult to detect factors associated with the observed changes over time. On balance, the evidence from the RECOVERY trial showing that dexamethasone reduces rates of

KRT in oxygen-requiring COVID-19 is more robust; the caveat is that the effects on biochemical AKI, which were not assessed in RECOVERY, are less certain.

Considerations regarding remdesivir are slightly different, because current RCTs do not report renal outcomes. Additionally, the mode of action of remdesivir (a nucleoside analogue that targets viral replication) differs from dexamethasone (which targets systemic inflammation), and whilst there is evidence for both having an effect on overall patient outcomes, it shouldn't be assumed that both will necessarily benefit renal outcomes. Forthcoming data from RECOVERY may help, with the possibility of contrasting the effect of anti-inflammatory approaches (dexamethasone, tocilizumab) on requirement for KRT with those of anti-virals (monoclonal antibodies casirivimab and imdevimab against the coronavirus spike protein). At present however, there is no evidence that shows remdesivir has a significant impact on the incidence of AKI or requirement for KRT.

The results of the study by Sullivan et al also posed some additional unanswered questions. It was notable that even after June 2020, there was a sizeable group of patients requiring oxygen who did not receive dexamethasone, despite this being recommended practice by that time. Reasons for this were unclear, but this may also play into the argument of unmeasured confounders. There was also a somewhat paradoxical observation that increased age was associated with a lower rate of AKI, which we can speculate may relate to differences in the threshold and primary reason for hospital admission across age groups.

In summary, this impressively large, multicentre prospective study that was carried out from the very start of the pandemic, confirms factors associated with COVID-19

associated AKI and receipt of KRT, and once again highlights the significantly increased risk of short-term adverse outcomes that the presence of AKI incurs. The fall in the rates of AKI and KRT over time is gratifying, but AKI remains a common complication of COVID-19. AKI should therefore remain an important focus for practitioners caring for hospitalised patients with COVID-19, and until more data is available, we should continue to pay attention to all of the possible contributing factors that may have led to these improvements.

CONFLICT OF INTEREST STATEMENT

None declared.

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