Dear Editor and Reviewer,

We would like to sincerely thank you for taking the time to review our manuscript and provide invaluable suggestions and recommendations. We have incorporated many of your recommendation. Some suggestion would perhaps be suitable to a more critical care inclined aspect of COVID 19 management rather than a nephrology point of view from the largest renal centre in Ireland. We will further discuss individual suggestions by the reviewer.

Response to individual suggestions:

Reviewer: "Kidney Injury in COVID 19" The title is appropriate, original and reflect the authors intension however, it is not very attractive to the readers at the first glance, I encourage the authors to search for more specific and catchy title.

Response: Thank you for your suggestion. We considered the title COVID 19 Associated Acute Kidney Injury, however majority of the authors in our centre preferred the title Kidney Injury in COVID 19. We do not believe this is a major issue and unless the editorial board wants to change the title we will continue with the same title.

Reviewer: Abstract: Concise, expressive and acceptable in the current format. I suggest the following to improve the abstract • ARDS came first as an abbreviation (need to write it).

Response: This was correctly pointed out and we have incorporated it in our abstract I.E Acute respiratory distress syndrome (ARDS)

Reviewer: Core tip: need to have a bitter flow or to come as points

Response: We have improved the flow of core tips as suggested by the reviewer.

Kidney injury in COVID 19 is associated with increased mortality with hypovolaemia, ARDS, cytokine storm and direct viral invasion having a prominent pathophysiological role. Haematuria and proteinuria is present in a high proportion of cases reflecting possible glomerular involvement and collapsing glomerulopathy has also been reported in genetically predisposed patients. This is further supported by autopsy findings showing SARS-COV-2 in proximal tubules and podocyte . Evidence supports a conservative fluid management strategy in COVID 19 associated ARDS with standard indications for renal replacement therapy. Hypercoagulation is a prominent feature leading to filter clotting thus regional citrate anticoagulation should be used. Kidney transplant recipients with COVID 19 should have immunosuppression reduced.

Reviewer: The authors should start with describing some numbers related to AKI incidence in Covid-19 and the mortality in this scenario. Covered in epidemiology • The introduction should include something about the pathophysiology as in general. 3) Hypothesis: • It is important for the reader to describe first how the authors define AKI in Covid-19

Response: We have further enhanced the introduction; however specific numbers are covered in the epidemiology section. The definition of AKI in the majority of the studies is based as per KDIGO guidelines. We have added this definition to the epidemiology section.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection leading to the coronavirus disease 2019 (COVID 19) is affecting millions of people worldwide more than 8,000,000 people, carrying a case fatality rate (CFR) between 0.9% to 7.2% depending on the demographics, implementation of preventative measures, testing strategies and availability of health care resources [1-3]. Severe disease is seen in approximately 20% of cases of which around 6% represents the critically ill COVID 19 patients [4, 5]. Amongst the critically ill, 65% to 95% have acute respiratory distress syndrome (ARDS), followed by acute kidney injury (AKI) and acute cardiac injury/ cardiomyopathy[6-8]. Emerging evidence suggests chronic kidney disease and acute kidney injury are independent markers of mortality in COVID 19[9]. AKI is common among critically ill patients with COVID 19 and is an independent marker of mortality[9, 10]. Prompt recognition and management of AKI in COVID 19 can limit its progression and contribute to reducing morbidity and mortality[10]. Multiple mechanisms of kidney injury have emerged as we learn more about SARS-COV-2[11]. In this review, we look to answer the Many pertinent questions remain regarding the epidemiology, pathophysiology and management of AKI in COVID-19 patients.

Reviewer : • The authors propose four main mechanisms for AKI in Covid-19, Hypovolemia, ARDS related AKI, Cytokine storm syndrome and direct viral invasion Also, these are the most common main mechanisms described in the literatures, but other mechanisms could exist as well that need to be adequately described as a review article a) ICU related causes including iatrogenic fluid restriction, high level of positive end expiratory pressure (PEEP), cardiac dysfunction and this is a wide category including left sided heart failure, right sided heart failure, myocarditis, and stress induced cardiomyopathy. The use of nephrotoxic drugs and this need description of the commonly used drugs

Response: Thank you for your suggestion. We have covered the various mechanisms described by the such as high PEEP, heart failure, vasoplegic shock etc under the section ARDS related AKI. The use of nephrotoxic drugs is commented on the risk factor section as it is general to any AKI rather than specific to COVID 19. Going into any further detail would not contribute to improving the article from a nephrology perspective rather change the emphasis on critical care and ARDS. We have referenced the entire section with high-quality studies which can be reviewed by individuals who are further interested in the topic. No other review to our knowledge from a nephrology perspective on COVID 19 have covered ARDS section in as much detail and we hope the reviewer kindly appreciated that.

We have added a possible mechanism of lung and renal injury which is more novel and involves hypoxia-inducible factor.

'..Impaired gaseous exchange with hypercapnia leads to a reduction of renal vasodilatory response, renal blood flow with altered diuresis and increased oxygen utilisation in the proximal tubule [39-41]. Severe hypoxemia also causes a reduction in renal blood flow with possible activation of hypoxia-inducible factor(HIF) system influencing lung and kidney outcomes[42]'

In the 'Risk Factor' section we have added a discussion on Remdesivir.

Drug dosing needs to be adjusted as per creatinine clearance and potential nephrotoxic treatment options need to be assessed for risk-benefit [111]. All drugs can cause acute interstitial nephritis and a high diagnostic suspicion is of paramount importance. Remdesivir, an antiviral drug has shown some evidence of quicker recovery and trend towards lower mortality amongst patient with severe COVID 19[112]. However, the drug is primarily renally excreted and is currently not recommended in patients with an estimated glomerular filtration rate (eGFR) below 30ml/min/1.73m2[113]. Animal models at high doses showed it can potentially cause AKI[113].

Reviewer: Miscellaneous mechanisms, due to association of severe cases of Covid-19 with other comorbidities including extremes of age, diabetes, hypertension, and gastrointestinal dysfunction

Response: Thank you for your suggestion. Gastrointestinal dysfunction is covered in hypovolemia section and then again in renal transplant section and other comorbidities in the risk factor section.

Reviewer: Rhabdomyolysis had been reported as an association and sometimes as an initial presentation of Covid-19 and this may lead also to AKI.

Response: The data regarding rhabdomyolysis is not consistent and no large cohort demonstrates it as a major mechanism. However, we do appreciate individual case reports showing its association thus we have incorporated the following: Preliminary reports suggest rhabdomyolysis is not a major component of COVID 19, but data varies in each centre with some case reports showing a significant rise in creatine kinase (CK) and other viral infections (H1N1 and SARS) have reported this complication[4, 61-63].

We did have a few cases of a rise in CK and possible rhabdomyolysis however our experience is consistent with larger cohorts that it is seen only in a minority of presentations. We could not incorporate primarily anecdotal evidence but did add case reports.

Reviewer: ARDS related AKI "The cardio-renal syndrome (CRS" the authors quoted from reference 59-64 this is not related to ARDS and needs to come under separate section like "cardiac reasons for AKI"

Response: Thank you for your suggestion. One of the main reasons to write this review article is also to make it educational, relatively easy to comprehend and remember particularly for fellows. As the number of categories is enhanced, it gives the perception of a long list which is not comprehensible, and we believe this where many review articles fail to deliver. The type of cardiorenal syndrome mainly seen in COVID 19 is type 5 associated with 'sepsis' and multiorgan failure. Majority of clinically relevant cardiac complications of COVID 19 happen in a critically ill patient with ongoing ARDS and it is often almost impossible to pinpoint what is the underlying primary pathology thus we felt it was appropriate to include in in this category. We have added an additional high-quality

reference discussing cardiorenal syndrome specific to COVID 19 {* reference 65 Apetrii M, Enache S, Siriopol D, Burlacu A, Kanbay A, Kanbay M, Scripcariu D, Covic A. A brand-new cardiorenal syndrome in the COVID-19 setting. Clinical Kidney Journal. 2020: 291 10.1093/ckj/sfaa082: 10.1093/ckj/sfaa082] }. However, we do agree that cardiac causes of AKI in relation to COVID 19 can equally be a separate section but this is a minor issue. We hope the reviewer kindly considers this.

Reviewer: The authors stated that "The overall combined effect of this entire process is an inflammatory, cardio depressant, acidotic, volume retaining state with high intrathoracic and intraabdominal pressures resulting in high renal back pressures, decrease and dysregulation of renal blood flow, and severe renal tubular injury." I do not know whether this comment is quoted from other references as there is no citation or this is the author's comment, if it is a the later it can not come under ARDS reason

Response: This statement is a summary of the ARDS and AKI section. The entire section is well referenced and the statement only summaries the content.

Reviewer: ) In the section direct viral invasion the authors stated that "Although hypertension is established as a risk factor for poor prognosis" I think there is new data removing hypertension link to poor prognosis, then the authors have to either mention this or to say hypertension is possibly linked to poor prognosis.

Response: We acknowledge the point of view of the reviewer and have changed the language and added a new reference.

Although hypertension may be a risk factor for poor prognosis with SARS-CoV2 infection, inferences that this is due to effects on ACE2 expression as a consequence of ACE inhibitor or angiotensin receptor blocker (ARB) use are not supported by data.

Reviewer: The authors quoted "Data from middle east respiratory syndrome (MERS), suggested the presence of the virus in the proximal tubular epithelial cells . I think the Covid-19 situation is extremely different from other respiratory viruses , so it is not wise to quote from the MERS in the same context until we have a full understanding of the situation.

Response: MERS is a type of coronavirus thus it is standard practice to review and compare with previously known similar pathogens and this is seen in other published literature. In our write up we compare SARS COV 2 with SARS COV and MERS, however provide evidence specific to SARS COV 2.

Reviewer: Risk factors, the authors adequately described the risk factors for AKI but again rhabdomyolysis which is not uncommon from the literatures and from the practical points of view was not described , the authors are aware of course that this problem needs to be highlighted as the management will be different from the trends towards fluid restriction which is followed in ARDS towards judged fluid management.

Response: Response: Thank you for your suggestion. As previously stated rhabdomyolysis is not very common particularly when assessing data from larger cohorts. Despite raised CK and AKI, most intensivist would base their management strategy based on pulmonary

status and if required would opt for CRRT rather than give high volume fluid replacement and potentially worsen pulmonary status.

We do appreciate that CK needs to be monitored and have mentioned it in risk factors.

'Urinalysis should be considered in conjunction with other baseline investigations such as FBC, renal profile, LFTs, D-Dimer, fibrinogen, ferritin, procalcitonin, LDH, IL-6, CRP, troponins, CK and SOFA score[72].'

Reviewer: Volume management, I think the authors need to know how they can monitor the volume status as the authors adequately escribed various volume management strategies, the first thing should be monitoring, whether it is enough to manage fluid non-invasively, by semi invasive technique or a complex invasive process is needed.

Response: This is an interesting point highlighted by the reviewer. However, we feel this is beyond the scope of this article as there is no consensus or RCT evidence regarding the best strategy to monitor volume, even for common bacterial septic shock. The practise varies from one centre to another and would require a full article to review this topic in detail. The details we have discussed on volume management are concise yet more extensive than any other review on COVID 19 in nephrology literature.

We did mention from a nephrology point of view the following:

'Both FACTT and FACTT lite protocols contained instructions to withhold furosemide until patients achieved a mean arterial pressure (MAP) of greater than 60mmHg for 12hours. However, specific fluid management in new-onset shock was not defined in both protocols. Despite its inaccuracies, targeting a central venous pressure (CVP) of around 8mmHg and pulmonary artery occlusion pressure of around 12mmHg with monitoring of urine output provided the best outcomes in both protocols[121, 122]. Volumes assessment is based on many other factors including passive leg raise response, inferior vena cava (IVC) diameter, lung ultrasound, ejection fraction, capillary refill time (CRT) and blood pressure (vasopressor requirement)'

We would once again like to thank the reviewer for his thought provoking suggestion and we tried incorporate these where possible and beneficial to the article. We hope for a timely editorial process as the world has now entered a second wave of COVID 19 pandemic, including Ireland, and further entering into unprecedented territory. We hope this article would benefit its reader and provide a valuable contribution the the literature.

Kind Regards,

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