

Kidney diseases and COVID-19 pandemic – A review article

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Abstract

In December 2019, an animal human coronavirus transmission occurred in Wuhan= China. A state of global pandemic was shortly declared, among a very rapid contagious spread of the virus. The causative virus was identified as SARS CoV 2 virus and is genetically related to the previous SARS outbreak in 2003. The virus causes wide clinical spectrum from mild flu like symptoms to adult respiratory distress syndrome. Kidney involvement has been reported in several reports in patients with various degrees of severity of SARS CoV2 infection. As knowledge is evolving, the accurate incidence of AKI is not known. Many questions are yet to be answered as regards the effect of epidemiological variables and comorbidities on the occurrence of AKI. Some reports have observed the occurrence of hematuria and proteinuria in a percentage of infected patients. Moreover, chronic kidney disease has not been found in some reports to add to the adverse outcomes, an aspect that merits further exploration. Patients on regular hemodialysis may be vulnerable to contagion due to lower status of immunity and need for frequent attendance to healthcare facilities. Due to the previous factors, prevention and mitigation of SARS CoV2 virus in this vulnerable population constitutes a major challenge.

Keywords

SARS Coronavirus; COVID-19;AKI;CKD

Introduction

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Origin and Epidemiology

SARS CoV 2 is a novel mutants of the coronavirus family that is causing the most recent and ongoing pandemic. The coronavirus is thought to have been transmitted at first instance from bats to humans. A wet wild animal market is likely considered the primary focus. The first cases of human infections were then reported in the city of Wuhan, the capital of Hubei province of China. This was followed by widespread of the pandemic to many countries around the globe. Till the time of writing of this paper (6th of April 2020), the number of infected people around the globe exceeded 1,300,000 patients with mortality over 74,000.

Pathogenesis

Covid-19 targets primarily the respiratory system causing wide clinical spectrum from mild symptoms to adult respiratory distress syndrome. The pathogenesis is mediated in severe cases through the so called cytokine storm (figure 1). This involves secretion of large amount of pro inflammatory cytokines and chemokines including IL8, IL 6, IL9, IL10 and many others. Pathogenic mechanisms to the kidneys are not fully elucidated, but suggested mechanisms are through attachment of the virus to ACE2 receptors. The excess secretion of cytokines leads to multiorgan failure in a percentage of patients, including AKI, through tissue hypoxia

Chronic kidney disease as a predisposing comorbidity in the event of Covid- 19

A number of studies have analysed patients' comorbidities. The prevalence of CKD was variable across studies ranging from 0.7 to 6.5% [27]. Only in one cohort of 710 patients, it was reported that 40% of patients had CKD in the form of deranged kidney function, hematuria or proteinuria [3]. Most studies that used regression analysis to predict poor outcome have not identified chronic kidney disease as an important prognostic factor [6]. The lack of stratification of CKD among the prognostic factors of SAR CoV, denotes that patients with CKD are not particularly at a higher risk of SAR CoV 2 infection [27][6].

Patients with end stage renal disease on hemodialysis have a lower immunity status to various types of infections. The impact of COVID-19 infection on haemodialysis patients merits further investigations. The only study involved 230 in Wuhan. During COVID-19 outbreak, 37 patients and 4 health care providers became infected. The clinical features of haemodialysis patients as reported in this cohort were mild. 7 deaths occurred among dialysis patients during the outbreak; however causes of death were not attributed to COVID-19[14].

AKI as a complication of Covid19

Acute kidney injury is a common complication of several infections. In the previous SARS CoV outbreak in 2003, the incidence of AKI was as low as 6% [16][4]. Nevertheless, AKI case fatality rate was high [10]. As for SARS CoV 2, the exact Incidence of AKI is not well known .Cohorts that reported AKI incidence among other patients characteristics are summarized in Table(1)[24][25][6,18][22][28][21][3][27][12][8][23][7][1][29][13]

There is heterogeneity among studies as regard the reported incidence of AKI. The reason for this heterogeneity may be attributed to inconsistencies in applying AKI definitions or due to genetic variability that merits further studies.

Some reports have shown that the incidence of AKI is significant, while others report that the incidence is marginal. Guan and colleagues have shown, in their large cohort of confirmed COVID 19 cases that the prevalence of AKI was as low as 0.5 %. This increased in patients with severe Covid 19 to 2.9%[6]. In other cohorts, incidence of AKI in confirmed cases of Covid 19 was higher.

In two cohorts the reported incidence of AKI was notably higher. In a cohort of 193 patients, the overall incidence of AKI was 28% and the incidence in severe cases was 66%[1]. In another cohort of 191 patients, the incidence of AKI in non survivors was 50% [29]. In the study by Hu and colleagues, AKI was present in 17 out of all 323 patients (5.3%) however, the incidence of AKI in patients with critical COVID-19 was 38.5%. also in this cohort most patients who had AKI(14 out of 17) had unfavorable outcome.

Interestingly, one retrospective study of 116 patients showed that the changes in kidney functions throughout the disease course were subtle[21]; this study included 5 patients on maintenance hemodialysis, all of them had severe disease but survived. In spite the subtle changes in kidney functions, none of patients in this cohort met the defining criteria of AKI, including seven deaths that were reported.[21] This report concluded that AKI and other kidney diseases are not of paramount clinical significance in patients with Covid 19.[21].

During previous SARS outbreak in 2003, a study of post mortem kidney biopsies, examined using electron transmission microscopy failed to detect any viral particles in kidney tissues. This finding supports the theory that most of kidney pathogenesis in of the earlier SARS outbreak was in the context of multi organ failure. The pathogenesis of AKI may be multifactorial. Suggested mechanisms are: direct cytopathic effect on kidney tissues as denoted by the retrieval of the viral RNA from urine samples [3]. The cytopathic effect of Covid 19 is now more evident as it has been shown that there is over expression of both

ACE2 receptors and a cleavage Spike protein in podocytes and proximal tubular cells.[15] This experimental evidence is of paramount importance and can explain proteinuria in patients with COVID-19. Interestingly, the latter experiment reports variable expression of cleaved S protein such that there is low expression in Chinese race as compared to Caucasians. Important pathological evidence was reported by Diao and colleagues. The pathology team managed to confirm the visualisation of the SARS CoV 2 viral particles in the renal tubular cells of post mortem kidney biopsies[5] [20]. The difference in kidney tropism between SARS CoV and SARS CoV 2 may be attributed to the affinity to ACE2 receptors in the kidneys.

Tissue hypoxia, in the context of massive cytokine secretion is a key nephropathogenic mechanism. Rhabdomyolysis and raised creatinine kinase have been observed in few cases [6]. It was also noticed in one cohort, that AKI occurs later to acute cardiac injury, suggesting a temporal relationship between cardiac injury and AKI and the possible occurrence of cardio renal syndrome [29]. In a recent single case report, collapsing variant of focal segmental glomerulosclerosis was diagnosed on renal biopsy of African American woman, which then tested positive to COVID-19. patient presented with confusion and rapidly deteriorating kidney functions, she improved markedly with the initiation of dialysis[11].

Hematuria and proteinuria

In the largest prospective cohort of kidney diseases in COVID-19, it was found that hematuria occurred in 26% of patients and proteinuria occurred in about 43 % [3]. This large prevalence of proteinuria could be explained by the finding of the above mentioned experimental study that showed that the expression of ACE 2 receptors in the podocytes and proximal tubular cells [15]. However, quantification of proteinuria, using 24 hour urinary collection or protein to creatinine ratio was not done within the investigation battery. Kidney

biopsy has not been attempted in any patients. In this prospective report, the presence of hematuria or proteinuria signaled poor outcome as measured by in hospitals mortality.

Effect of dialysis modalities on survival in patients infected with Covid-19

Continuous renal replacement therapy is a modality of dialysis that implies increasing the clearance of solutes through convection, diffusion, ultrafiltration and adsorption. The modality has benefits in critically ill patients, including removal of septic toxins in addition to correction of the uremic status. There is accumulating evidence that critically ill patients that develop AKI may have lower mortality if they are treated using CRRT[17].

As knowledge is evolving about SARS CoV 2 virus, the benefit of CRRT in the management of critically ill patients with Covid-19 is much less clear. One retrospective study was conducted in China on 36 confirmed covid-19 cases who have been admitted to the intensive care unit [25]. All patients were mechanically ventilated and the aim was to compare the effect of continuous renal replacement therapy (CRRT) as compared to conventional dialysis. Patients were followed up for an average time of 10.4 days. The mean serum creatinine was slightly higher in patients who received CRRT than patients who did not receive CRRT (94.5 mmol versus 72 mmol, $p=0.017$). There was marginal favorable effect of CRRT in terms of adjusted mortality (54.4% in CRRT group versus 78% in the conventional hemodialysis group).

On the contrary, another analysis of risk factors and survival in critically ill patients found that non survivors received more treatment with CRRT than survivors.

Another study of 101 case fatalities in China, 5 cases had CRRT . 2 patients who died within 3 days and 3 patients who died after 3 days. The mean baseline serum creatinine was 139.8 μmol [19]. In another large retrospective analysis by Guan and colleagues, 9 patients treated were treated by CRRT , 8 of which died which signifies that CRRT had no mortality

benefit[6]. In a cohort of 191 patients, 10 patients received renal replacement therapy, they all did not survive, suggesting that renal replacement therapy in severe cases of Covid 19 may not have any survival benefit.[29]

Renal specific mortality due to Covid 19

The leading causes of mortality in COVID-19 infected patients are sepsis and ARDS. This has been observed in several cohorts. In a large prospective study, it was shown that the development of AKI in patients infected with Covid-19, was associated with four fold increase in the mortality [3]. In other reports, renal specific causes were not the most common or the second most common of mortality of COVID- 19. In a retrospective study of 101 non surviving COVID-19 patients, the incidence of AKI was 23%, there was no significant difference between patients who died within 3 days and patients who died later as regards AKI incidence (25% versus 21%, $p=0.611$)[19]. In this cohort AKI was the 3rd leading cause of death after respiratory and cardiovascular causes. In a single centered study in China, Chronic kidney disease was present in 7 out of 323 patients (2%)., 4 patients and 3 had non severe disease .The elevation of of BUN > 88 mmol/L was associated with 2 fold increase in the chance of poor clinical outcome. Baseline serum creatinine of less than 88 mmol/L was associated with 63% reduction in the development of poor outcome. In another report of 82 non surviving patients with confirmed Covid-19, the AKI percentage was 31%[26].

Prevention and mitigation of Covid 19 among dialysis patients

Up till the time of writing of this paper, there is no consensus and formal approval of any medication for COVID -19. This fact mandates exhausting all measures to prevent the transmission of infection. In this respect, The centers for disease control and prevention (CDC) have issued an interim guideline for hemodialysis centers. The guideline emphasizes

the importance of early recognition and isolation of cases while attending their scheduled sessions [9]. This mandate treating confirmed cases of Covid-19 hemodialysis in designated rooms with droplet infection prevention precautions; patients with confirmed or suspected Covid 19 should be separated by 6 feet distance. The instructions for hemodialysis patients should be centralized around reporting any new symptoms of fever, cough. Patients should be instructed on the proper use of face masks and using tissues when sneezing or coughing to prevent spread of infections [2,9]. There is an anticipated extraordinary strain on hemodialysis facilities. In parallel, there are a number of suggestions to match the resources. These practical suggestions aim at reduction of the strain on hemodialysis units [9]. One of the possible suggestions is changing the dialysis regimen from three times weekly to twice weekly.

Conflict of interests

TA declares no conflict of interest.

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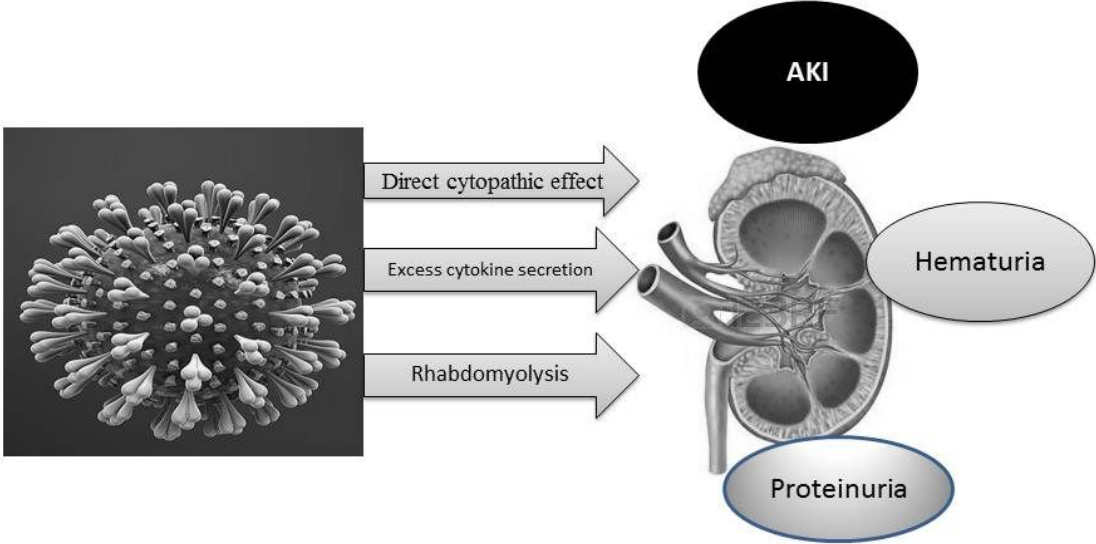


Fig.1 Renal complications of SARS
CoV 2 virus

Author Name	Number of patients	Study design	AKI percentage(all)	AKI percentage (non severe cases)	AKI percentage (severe cases)	significance	CKD at baseline	Baseline BUN (non severe cases)	Baseline BUN (severe cases)	Baseline creatinine (severe cases)	Baseline creatinine (non severe cases)	significance	mean BUN (non severe cases)	mean BUN (severe cases)	mean creatinine (non severe cases)	mean creatinine (severe cases)	significance	comment
Luwen Wand et al	116	retrospective	7/116	Not reported	Not reported	NA	4.3% on CRRT											7 deaths had no AKI patients on CRRT survived
Shijiao Yan et al	168	retrospective	3.6%	0%	8.30%		0.6%						3.6	4.1	62.1	57.3		AKI was the 3rd leading cause of death
Yi Yang*	36	retrospective	22.0%	Not reported	Not reported													CRRT made no difference of death at 3 days
Guo-Qing Qian	91	retrospective	3.0%	Not reported	Not reported		Not reported						3.9	5.8	66	81		
Yafei Wang,	110	retrospective											3.93	4.99	55	74	significant	
Zonghao Zhao	75	retrospective	20.0%	Not reported	Not reported	NA	5.3%								67	72.5		significant difference in serum creatinine between patients with severe pneumonia and patients with mild illness
Luwen Wang ***	116	retrospective	7.2%	Not reported	Not reported	NA	4.3%											5 hemodialysis patients received CRRT and all of them had severe infection but survived
Guan et al***	1099		5% all and 2.9% in severe cases	0.1	2.9	NS	0.7%											
Yichun Cheng	710	Prospective	5.1%				Abnormal kidney function in about 40%											Hematuria(26%) and proteinuria(40%)
Wen Zhao	77	Retrospective	2.6% NS between severe and non severe			NS	6.5%,NS between severe and non severe			68	63	NS						No significant difference between severe and non severe cases as regard baseline serum creatinine
Jiatao Lu	577	retrospective	3.0%	2.8	3.3	NS				65.5	64	NS						cutoff value of serum creatinine 77 was associated with 2.9 odds ratio
Huang Huang	125 severe Covid	Retrospective		Not reported	Not reported					64	77.5	NS						Nor AKI or CKD were identified as a prognostic factors
Jianfeng Xie	444	Retrospective								66	85	0.001						there was significant difference in baseline creatinine between patients who survived
Ling Hu	323	retrospective	5.3%	3.3	38.5	0.007	2.2%											
Zhen Li***	193	retrospective	28.0%	9%	66%					73	63							
Fei Zhou	191	retrospective	15.0%		50% in non survivors	Significantly higher in non survivors	1.0%											10 patients had renal replacemnet therapy and they all did not survive
Kun-Long Ma	84 severe cases	retrospective	7.1%	1.60%	25%	0.003	1.2%											

Table (1) characterization of renal complications in several cohorts

