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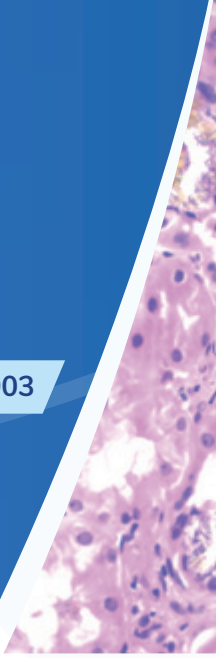


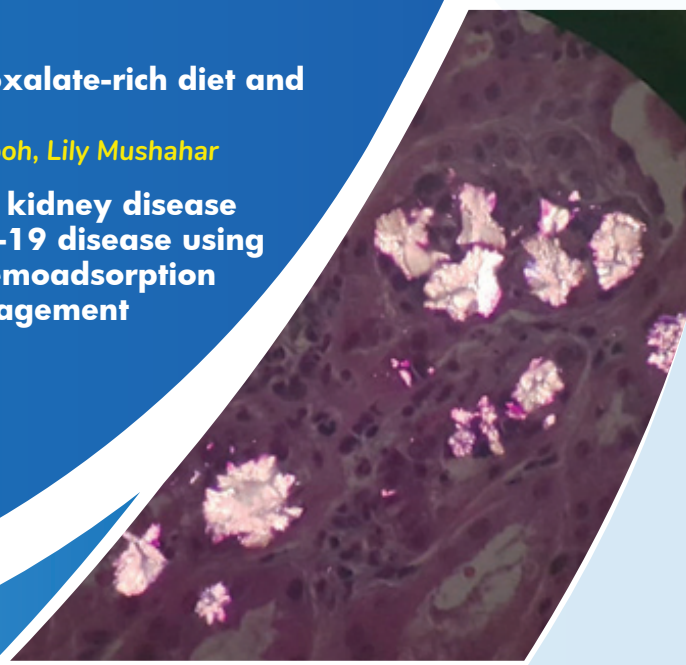
Editorial

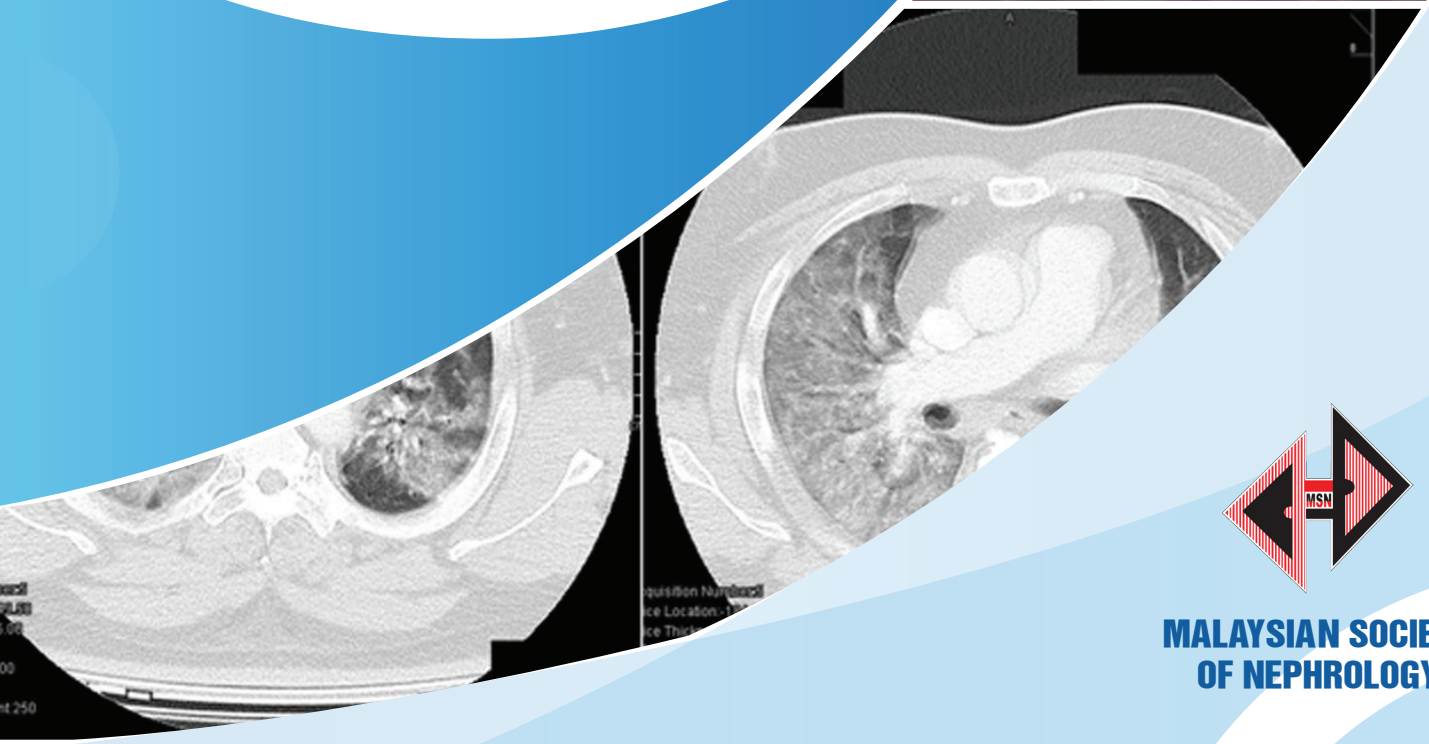
1. **Acute Kidney Injury in Covid-19 Infection: A Qualitative Review of Literature**
   >> *Xue Meng Lim, Christopher Thiam Seong Lim*

Case Report

1. **Oxalate nephropathy secondary to oxalate-rich diet and excessive vitamin C Intake**
   >> *Siti Hafizah Mohammad Ismail, Roslina Suboh, Lily Mushahar*

2. **Successful treatment of an end-stage kidney disease patient presenting with severe Covid-19 disease using enhanced cytokine removal with haemoadsorption therapy in addition to standard management**
   >> *Esther Zhao Zhi Tan, Hin Seng Wong*





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Editorial

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ACUTE KIDNEY INJURY IN COVID-19 INFECTION: A QUALITATIVE REVIEW OF LITERATURE

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ABSTRACT

COVID-19 is a coronavirus infection of the respiratory system, with multiorgan involvement. Acute kidney injury (AKI) is one of the complications of covid-19 infection. This review explored the epidemiology, pathophysiology, risk factors, and outcome of AKI in Covid-19 infection. There is huge variability in the incidence of AKI among COVID-19 patients from different regions of the world. Some modifiable and non-modifiable risk factors that can increase a patient's risk of developing AKI have been identified. Mortality is significantly increased if a COVID-19 patient develops AKI. Avoidance of risk factors and improve survival and reduce morbidity among patients. Long term follow up is recommended for survivors with AKI to monitor for future kidney disease.

Keywords: *Acute kidney injury, COVID-19*

INTRODUCTION

COVID-19, which was first described in December 2019, has since been declared a pandemic in March 2020 by the WHO, and has caused a significant worldwide morbidity and mortality. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The gold standard for diagnosing infection is by identification of SARS-CoV-2 RNA in respiratory tract secretion saliva by real-time polymerase chain reaction, but other methods such as detection of viral antigen and antibody production against the virus have been used for diagnosing COVID-19 infection as well [1, 2, 3]. The route of human-to-human transmission is through inhaled respiratory droplets and direct contact [4, 5, 6]. The median incubation period for the virus is 5.1 days, with symptoms mostly developed within 11.5 days [7]. Clinical features of the disease have been reported as a wide spectrum, from asymptomatic infection to mild respiratory tract symptoms to viral pneumonia, and finally multiorgan failure and death at the end of the spectrum.

The main system implicated in this disease is the respiratory system, but other systems such as the kidneys are also affected, especially in severe diseases. Epidemiological studies have pointed out several factors which increased one's susceptibility to symptomatic and severe disease, such as older age, metabolic syndrome, diabetes and cardiovascular disease [8]. The presence of end-organ damage such as lungs or kidneys increased the risk of mortality [8]. Patients with COVID-19 develop more severe acute kidney injury (AKI), require more dialysis and are less likely to have inpatient renal recovery compared to patients without COVID-19 [9], hence predisposing them to new onset or progression of chronic kidney disease [10]. This review study aimed to explore in-depth and to bridge the knowledge gap regarding AKI in COVID-19 disease.

METHODOLOGY

The aim of this systematic literature review was to review evidence regarding AKI in COVID-19, focusing on incidence, pathophysiology, risk factors, and outcome. A systematic search was conducted in PubMed/MEDLINE, Scopus and Cochrane Center Trials databases to identify all

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JCTN (2022) Volume 1: Article no: 1

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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publications on AKI in COVID-19 patients. Search terms such as "COVID-19", "Coronavirus", "SARS-CoV-2", "Severe Acute Respiratory Syndrome Coronavirus 2", "acute kidney injury", "acute renal impairment", and "acute renal failure" were used. All articles from 1st December 2019 to 12th January 2022 were included. All relevant literature and their reference lists were reviewed by two independent reviewers using inclusion and exclusion criteria. The inclusion criteria included case reports, case series, prospective and retrospective cohort studies, systematic reviews, and meta-analyses assessing AKI in adult COVID-19 patients. Animal studies, letters, studies on kidney transplant patients, studies with only abstract published, and studies not in English were excluded. As this is a qualitative review, there is no statistical method involved.

EPIDEMIOLOGY

There are variable ways studies define AKI in COVID-19 patients. AKI is defined by Kidney Disease Improving Global Outcomes (KDIGO) as an increase in serum creatinine by > 26.52umol/L or increase in serum creatinine > 1.5 times from baseline, or a reduction in urine to < 0.5 mL/kg/hour for six hours [11]. It is further divided into Acute Kidney Injury Network (AKIN) stages based on serum creatinine level changes. Another way of defining AKI is using the Acute Dialysis Quality Initiative (AQDI) RIFLE criteria, which specify degree of kidney impairment (risk, injury and failure), and outcome (loss and end stage kidney disease). Some studies defined AKI based on two-fold increase in serum creatinine between baseline and peak level during hospitalisation.

A meta-analysis consisting of 39 clinical studies on AKI n COVID-19 infection reported incidence of 15.4%, which increased to 53% among patients with severe COVID-19 infection, and 4.3% of these patients required some form of kidney replacement therapy (KRT) [12]. Another larger meta-analysis consisting of 79 studies from Asia, North America and Europe described an incidence rate of 10.6%, and that those with more severe disease were more likely to require continuous KRT [13].

A systematic review of sixty studies from China, the USA, Korea and Europe recorded a 19.45% pooled incidence of AKI in COVID-19 patients, and KRT requirement incidence among COVID-19 patients with AKI at 39.04% [14]. In a separate systematic review, which included

Study	Type of study	Region	Studies number	Sample size	Median age (years)	CKD included?	AKI
Fabrizi et. al.,[12] 2020	Systemic review & meta-analysis	China, USA, Korea	39	25566	61	Yes	15.4%
Lin et.al.,[13] 2020	Meta-analysis	China, USA, Europe, Kuwait, Mexico, Iran, Hong Kong	79	49692	N/A	N/A	10.6%
Raina et. al.,[14] 2021	Systemic review	China, USA, Korea, France, UK	60	42612	61.1	Yes	19.45%
Xu et.al.,[15] 2021	Systemic review	China, USA, Korea, Europe, Singapore, Japan	22	16199	61.2	N/A	10%
Zheng et.al.,[16] 2020	Systemic review	China	25	10419	56	Yes	6.5%
Sundaram et. al.,[17] 2021	Retrospective cohort	India	1	110	61	N/A	28.2%
Hirsch et. al.,[18] 2020	Retrospective cohort	USA	1	6477	AKI: 69 Non AKI: 61	N/A	36.6%
See et. al.,[19] 2021	Retrospective cohort	Singapore	1	707	46	N/A	8.1%
Chan et. al.,[20] 2021	Retrospective observational	USA	1	3993	64	Yes	46%

Table 1: Incidence of AKI in COVID-19 patients.

N/A = Not available

JCTN (2022) Volume 1: Article no: 1

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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22 studies from China, the USA, East Asia, Europe and Singapore, the incidence rate of AKI was recorded at 10% and among these patients, 4% required KRT [15]. Another systematic review including 25 studies only from China showed a pooled incidence of AKI in COVID-19 patients at 6.5%, with increased incidence in intensive care units at 32.5% [16].

A retrospective cohort study consisting of 110 hospitalised COVID-19 patients in South India reported a 28.2% incidence of AKI [17]. This is lower than that found in a retrospective cohort study conducted in the USA, which reported an incidence of 36.6%, among which 14.3% required KRT [18]. This study also showed an increased rate of AKI among ventilated patients at 89.7%, versus non ventilated patients at 21.7%. Nearer to home, a retrospective cohort study from Singapore recorded an even lower incidence of AKI among COVID-19 patients at 8.1%, possibly due to younger median age among the patients [19]. A retrospective observational study conducted in the USA showed that the incidence of AKI was 46% among COVID-19 patients [20].

In Malaysia, the average 7-day incidence rate of COVID-19 was reported to be at 26.6 per 100000 population [21]. AKI was reported at 4% among COVID-19 patients in Malaysia [22].

From these studies and analyses as summarized in Table 1, we know that the incidence of AKI among COVID-19 patients were between 6.5% to 46%, with a lower incidence among Chinese patients and highest among those in the USA. This can be explained by the different criteria for hospitalisation, by which the China healthcare system isolated and hospitalised all positive patients whereas the USA healthcare system admitted those who are significantly more ill and require intervention or treatment.

PATHOPHYSIOLOGY

Coronaviruses are enveloped RNA viruses with a nucleocapsid. SARS-CoV-2 is made up of four main structural proteins, namely the surface spike which resembles a crown, envelop glycoprotein, nucleocapsid and membrane proteins, as well as 16 non-structural proteins [23]. The virus enters the host cell via the binding of its spike protein to the host angiotensin 2 (ACE2) receptors and then priming by the host transmembrane serine protease 2 (TMPRSS2). After entry, the virus is replicated by endocytosis and virion assembly [24]. There are two stages of SARS-CoV-2 pathogenesis, namely the earlier viral replication phase, followed by host cell immune response to the infection via inflammatory cells recruitment and cytokine release.

1. Direct tissue invasion and role of ACE2

Various studies implicated the effect of direct viral invasion and injury to the renal tissue. In a post-mortem biopsy of a COVID-19 patient with renal failure, there was virus visualization and isometric vacuolization of proximal tubules [25]. Post-mortem renal biopsy of 26 patients found SARS-CoV-like particles and its positive antibody staining in the renal tubules, supporting the pathophysiology of direct viral invasion to renal tissues [26]. An autopsy of nine patients in the UK reported acute tubular injury in all biopsies, real-time PCR targeting viral E gene was found positive in three patients, and one sample showed positive sub-genomic viral RNA [27, 28]. Renal tissue viral tropism is further supported by a study that isolated SARS-CoV-2 from post-mortem kidney tissue, demonstrating the virus ability to replicate in non-human primate kidney tubular epithelial cells [29]. This same study identified a higher frequency of viral RNA in kidney tissue among patients with AKI compared to those without. Another post-mortem renal biopsy of six patients reported acute tubular necrosis, sloughing of luminal brush border, vacuole degeneration and detection of viral antigen via immunohistochemistry [30]. SARS-CoV-2 particles have been found in urine samples [26, 31], which could be explained by the viral release into the tubular lumen from the damaged tubular epithelial cells, as the large virus size reduces the likelihood that it underwent glomerular filtration [32].

ACE2 receptors and the host TMPRSS2 play a significant role in the pathogenesis of AKI in COVID-19 infection by serving as a target for viral attachment. In vitro cell study demonstrated the attachment of glycoprotein spikes on the surface of SARS-CoV-2 to ACE2 and entry into cell; the spike protein is cleaved by cellular TMPRSS2 causing the release of fusion peptides leading to membrane fusion [33, 34]. Co-expression of ACE2 and TMPRSS genes in the kidneys has been reported in proximal tubule brush border apical membrane and podocytes in the kidney [35, 36]. Post-mortem renal biopsy results of 26 patients showed diffuse acute tubular injury as evidenced by the loss of brush border, vacuolar degeneration, and tubular lumen dilatation containing cellular debris, besides endothelial injury and distinct expression of ACE2 in proximal tubular cells especially around areas of severe injury [26]. Diffuse polymorphonuclear casts in the tubule lumens and multiple bacterial foci. Erythrocyte stagnation in glomerular capillary loops and peritubular areas without fragmentation of red cells or thrombi was also described [26].

JCTN (2022) Volume 1: Article no: 1

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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In COVID-19 infection, angiotensin II is increased [37] causing downregulation of ACE2, which leads to activation of type 1 angiotensin receptor activation, decreased formation of angiotensin 1-7 and worsening of AKI [38]. Angiotensin II reduction, with its subsequent increase in renin through a positive feedback loop, has been demonstrated in COVID-19 patients with AKI [39, 40], leading to poor outcomes in critically ill patients [41, 42]. However, inhibition of the renin-angiotensin-aldosterone system (RAAS) is not associated with an increased risk of hospitalisation or severe disease in COVID-19 patients [43].

2. Systemic inflammation and role of cytokines

Systemic inflammation and cytokine storm have been described to be another mechanism through which AKI develop in COVID-19 patients. Patients with AKI showed increased inflammatory markers such as ferritin, D-dimer, erythrocyte sedimentation rate, procalcitonin and C-reactive protein, signifying the role of inflammation in kidney injury [44, 45, 46]. In severe disease, immune overactivation leads to cytokine storms, causing systemic inflammation [47]. COVID-19-associated macrophage activation and cytokine storm lead to tissue factor release and coagulation factor activation, resulting in a hypercoagulable state [48]. A study also reported strong complement C5b-9 (membrane attack complex) deposition in the renal tubules of COVID-19 patients, suggesting the role of complement pathway activation in inflammatory cascade and procoagulant state [30]. Another study detected C3c and C3d in glomerular capillaries and renal arteries, C3d in the tubular compartment, as well as C5b-9 in peritubular capillaries tubular basement membrane and arterioles [49]. Activation of the complement system leads to inflammatory response, vascular damage and coagulation. However, the cytokine storm mechanism has been challenged by shreds of evidence of lower interleukin-6, interleukin-8 and TNF levels in COVID-19 patients compared to sepsis patients and those with non-COVID ARDS [50, 51], which suggest that inflammation is a contributory factor in kidney injury rather than the main mechanism.

3. Glomerulonephritis

Renal biopsy data from 47 patients in a study based in France reported that the majority of AKI in critically ill patients were of tubular origin, and who were not critically ill had collapsing glomerulopathy and focal segmental glomerulosclerosis [52]. Although the pathophysiology of collapsing glomerulopathy in COVID-19 is unknown, it has been postulated to be similar to HIV-associated nephropathy, via podocyte injury through autophagy and mitochondrial disturbances [53]. Collapsing glomerulopathy and thrombotic microangiopathy have also been reported in COVID-19 patients by others [54, 55].

Some of these histological abnormalities are found in patients without an increase in serum creatinine or oliguria, signifying a cellular level of injury occurring in COVID-19 patients without disrupting clinical renal function. Besides increases in serum creatinine, other reported renal manifestations include proteinuria, hematuria, hyperkalemia, hyponatremia and metabolic acidosis [56, 57, 58]. A systematic review reported pooled proportion of proteinuria among COVID-19 patients at 52.47% and that of hematuria in the patients at 35.89% [14]. However, low molecular weight proteinuria rather than albuminuria has been reported by a study, signifying tubular injury instead of glomerular [59].

4. Prothrombotic state and other contributing factors

A few other publications reported that besides the mechanisms of AKI described above (cytokine storm, complement dysregulation, activation of angiotensin II pathway), nephrotoxic treatments, respiratory distress causing hypoxia, hypovolemia, prothrombotic state of the disease and nosocomial sepsis could contribute to the development of renal injury among COVID-19 patients [38, 60, 61, 62]. Renal artery thrombosis has been reported in some case studies [63, 64]. To summarize, the pathophysiology of AKI in COVID-19 is multifactorial and often, injury begins at the cellular level before renal function impairment clinically.

RISK FACTORS AND PREDICTORS

Various studies and analyses have described some risk factors for the development of AKI among COVID-19 patients. A meta-analysis study reported that age 60 years and above had a higher risk of AKI with an odds ratio of 3.53 and the risk of AKI with the severe disease showed an odds ratio of 6.07 [13]. Listed here are some factors that predisposed patients to higher risk of developing AKI in the course of the disease.

1. Baseline characteristics

Older age [12, 13, 18, 65, 66, 67, 68], male gender [18, 68, 20], and black race [18] have been associated with higher risk of developing AKI in COVID-19 disease.

2. Comorbidities

COVID-19 patients were reported to be at higher risk of developing AKI if they have following comorbidities such as increased body mass index [68, 69], chronic habit of cigarette smoking [68], hypertension [18, 65, 68], diabetes mellitus [18, 68], cardiovascular disease [18, 65, 68, 69], premorbid respiratory disease [18], premorbid chronic kidney disease [66, 67, 68, 20, 70, 71, 72], arterial hypertension [12] and cancer [68].

3. Disease characteristics

Some of the predictors of the development of AKI in COVID-19 disease include disease severity [13, 19, 65], higher baseline inflammatory markers [67, 72, 73] and usage of mechanical ventilation [18, 68, 72]. Concurrent presence of hematuria and proteinuria are strong predictors of the development of AKI [17], and the more severe these urinary abnormalities were, the higher the mortality rate [38, 45].

4. Medications

Medications usage that were associated with higher risk of AKI are vasopressor medication [18, 68], baseline usage of medications inhibiting the renin-angiotensin-aldosterone system [19] and nephrotoxic medications (vancomycin and nonsteroidal anti-inflammatory drugs) [19]. However, the discontinuation of inhibitors of renin-angiotensin-aldosterone system did not affect the disease severity of COVID-19 or renal functions [74].

Treatment in a tertiary hospital was found to imperceptibly reduce the risk of AKI [18]. The presence of AKI increases the risk of requiring mechanical ventilation [75]. Some of the predictors of mortality include age, male gender, diabetes, cerebrovascular disease, more than two-fold increase in serum lactate dehydrogenase, and degree of severity of AKI [76].

OUTCOME

There are three main outcomes of AKI in COVID-19 patients, namely recovery of renal function, progression to chronic kidney disease and death.

One study reported that only 30% of patients with AKI had renal recovery at discharge [20]. Complete renal recovery of 81.7% and partial recovery of 17.2% upon discharge among patients with AKI in COVID-19 was reported, with worse outcomes in more severe kidney injury and those with premorbid chronic kidney disease [76]. Another study found that among the survivors, the incidence of chronic kidney disease was 15% three months after suffering AKI during COVID-19 infection [77]. A retrospective cohort study consisting of 1612 patients documented that the patients with COVID-19 who developed AKI during hospitalisation had estimated glomerular filtration rate decline by 11.3 mL/min/1.73m2 per year faster compared to non-COVID-19 patients who had AKI from other illnesses [78].

Meta-analysis involving 49692 patients reported an increased risk of death in COVID-19 patients with AKI, with an odds ratio of 11.05. Continuous KRT is predictably required significantly more in severe disease, with an odds ratio of 6.6 [13]. Another meta-analysis also showed the increased mortality among patients with AKI, with an odds ratio of 15.4 [12]. One systemic review found that the mortality among patients with acute renal impairment to be higher at 54.24% versus 17.71% overall [14]. Similarly, in another study mortality was reported to be at 50% among hospitalised COVID-19 patients with AKI [20]. Ninety-day mortality of 31% was documented in a prospective cohort study, with increased mortality among the elderly, obese, diabetic, and severe ARDS patients [79]. A retrospective cohort study in India of 110 patients reported a mortality rate of 24.5% with a strong association between AKI and death [17], whereas a study in Turkey demonstrated a mortality rate of 38.9% [76].

DISCUSSION

COVID-19 is a worldwide pandemic disease with AKI as a significant complication that increases mortality risk. Vaccination and reduction in human contact are among the current prevention measures for COVID-19. The incidence of AKI among COVID-19 patients varied from 6.5% to 46%. This huge variation can be attributed to the patients selected for studies; the degree of disease severity among the hospitalised patients has to be taken into account. The majority of the publications reviewed reported the incidence of AKI in hospitalised COVID-19 whereas a significant proportion of patients who underwent non-healthcare setting quarantine or self-monitoring were under-represented by these data.

SARS-CoV-2 has been shown to directly invade and cause injury to the renal tissues with predilection at the tubular cells. Other mechanisms of injury include inflammation, cytokine storm, complement dysregulation, activation of angiotensin II pathway, nephrotoxic agents, hypoxia due to respiratory distress, hypovolemia, prothrombotic state of the disease and nosocomial sepsis. The list is non-exhaustive and is still under study.

Several risk factors have been identified to predispose

COVID-19 patients to AKI. Identification of the non-modifiable risk factors such as older age, male gender and black race increases the awareness among the healthcare provider towards population at risk. The increased mortality among elderly patients and in those with premorbid illnesses can be due to reduced renal functional reserve, decreased functioning renal mass and diminished stress-induced renal capacity to increase its glomerular filtration rate [80]. Modifiable risk factors such as pre-morbidities especially chronic kidney disease and nephrotoxic treatment or medications should be avoided especially among the at-risk patients, to lower the chances of developing AKI. Future studies on the early markers of AKI in COVID-19 will be required to identify patients with renal cellular injury from the disease before it progresses to clinical renal function impairment.

Treatment for COVID-19 has not been reviewed in this publication due to its ever-evolving nature involving various ongoing clinical studies. The mainstay treatment for COVID-19 disease is a steroid, and a study showed that steroids improved the chances of renal function recovery after an acute injury [81, 82]. Besides steroids, current management for AKI in COVID-19 is mainly supportive, with the use of KRT when indicated which is tailored to the haemodynamic status of the patients [83]. Volume repletion, avoidance of nephrotoxic medications and treatment of sepsis are among the supportive management given to these patients. When required, standard protocol and prescription for continuous KRT can be given to the COVD-19 patients with AKI as per those without COVID-19 as studies have shown no difference in circuit patency and effectiveness of the therapy, with personal protective equipment and proper disinfection between use [84, 85, 86]. Clinical trials on extracorporeal cytokine removal treatment are ongoing.

From our review, only a portion of AKI patients recovers to baseline creatinine before discharge, with some reported delayed renal recovery during outpatient follow up [68]. There were a number of these survivors who went on to develop chronic kidney disease and renal failure. Failure of renal function recovery to baseline has been associated with increased mortality and subsequent chronic kidney disease [87]. This highlights the importance of long term follows up for the patients who developed AKI during COVID-19 disease regardless of renal function upon discharge.

Vaccination efforts against SARS-CoV-2 have been made worldwide as a preventive measure to limit COVID-19 contagion and mortality. Several case reports found de novo minimal change disease (MCD) and AKI following vaccination [88, 89, 90, 91], as well as relapse of MCD post vaccination [92, 93]. Besides MCD, other glomerulonephritis with AKI has been reported following COVIDd-19 vaccination include IgA nephropathy, focal segmental glomerulosclerosis, anti-glomerular basement membrane nephritis and NELL-1-associated membranous nephropathy [94, 95, 96]. AKI associated with PR3-ANCA vasculitis [97] and MPO-ANCA vasculitis [98] have also been reported following vaccination. These reports involved both messenger RNA-based and adenovirus vector-based vaccines, and it has been postulated that immune mediated mechanisms mimicking natural response to COVID-19 infection may have lead to the injury, although there is no concrete evidence available currently on the pathophysiology of vaccine-related AKI. As current evidence shows overwhelming benefits of COVID-19 vaccination in preventing severe disease and death, nevertheless, physicians should be aware of the possible rare association between the acute flare of renal disease and vaccination.

The strength of this review is that it contains a summary of various aspects related to AKI in COVID-19 disease. The weakness of this review is that it is a qualitative review that did not involve statistical analysis of the data. We also did not review treatment of AKI in COVID-19 in detail, as there is sparse variability of evidence-based treatment besides that discussed above. COVID-19 has been a worldwide disease burden since the end of December 2019, and there is much room for improvement in terms of knowledge for this disease.

CONCLUSION

COVID-19 pandemic worldwide has led to significantly high morbidity and mortality. AKI is prevalent among hospitalised patients, especially among those critically ill. Studies have shown worse outcomes among patients with adverse kidney involvement. Risk factors have been identified, which may help stratify at-risk patients, prioritize monitoring and initiate preventive measures. Long term follow-up among the survivors with or without renal recovery is advocated because of their increased risk for subsequent chronic kidney disease and worsening of premorbid renal impairment.

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JCTN (2022) Volume 1: Article no: 2

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Editorial

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OXALATE NEPHROPATHY SECONDARY TO OXALATE-RICH DIET AND EXCESSIVE VITAMIN C INTAKE

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ABSTRACT

Oxalate nephropathy is a rare condition but remains an important cause of end-stage kidney disease. A 42-year-old man with no comorbid was referred to a nephrologist because of worsening kidney function (serum creatinine from 290 to 836 µmol/l) for the past 3 months. He was found to have impaired renal function when he was treated for pneumonia. The initial workup was unrevealing. Within a couple of weeks after the first visit, he became symptomatic with nausea and vomiting. Further history revealed that he had sought alternative treatment with numerous supplements containing high doses of vitamin C and ingesting foods with high oxalate precursor. A kidney biopsy was performed and confirmed oxalate nephropathy. Despite restriction of oxalate consumption, his kidney function deteriorated and he was initiated on long term hemodialysis.

Keywords: *Acute kidney injury, oxalate nephropathy, vitamin C*

INTRODUCTION

In the modern health-conscious world where one believes in the power of superfoods or supplements, it is not surprising that many tend to overdo with specific type of diet or harping on extra supplements for general well being. Consumption of extremely high levels of certain nutrients is detrimental to the body. We reported a case of secondary oxalate nephropathy from excessive consumption of vitamin C and oxalate-rich diet leading to the development of end stage kidney disease.

CASE REPORT

A 42-year-old Malay man with no comorbid was referred to our nephrology clinic because of worsening kidney function. He complains of nausea and vomiting for one-week duration. He had no fever, diarrhea or abdominal pain. There were no urinary symptoms or prior history of kidney stones. He had no constitutional symptoms or usage of non-steroidal anti-inflammatory drugs. He had been taking multivitamins daily for many years. He has no family history of kidney disease or kidney stones. He does not smoke or drink alcohol.

On further history, he was admitted to a district hospital two months earlier and was treated for pneumonia complicated with acute kidney injury. There were no reports of hypotensive episodes during his hospitalization. On admission, his laboratory studies showed elevated white cell counts at 19 x 103/uL, platelet of 245 x 103/uL, hemoglobin of 10.9 g/dl, urea nitrogen level of 23 mmol/L, and serum creatinine level of 552 µmol/L. Serum electrolyte results included the following values: sodium, 138 mmol/L; potassium, 4.2 mmol/L; chloride, 110 mmol/L; bicarbonate, 16 mmol/L; glucose, 8.4 mmol/L; calcium 2.2 mmol/L and phosphorus of 1.7 mmol/L. Urinalysis revealed proteinuria of 2+.

Blood cultures grew *Klebsiella pneumoniae* and he was treated with intravenous antibiotics and hydration. He responded to treatment and was discharged well with improving kidney function. Upon discharge, his urea nitrogen level improved to 14 mmol/L and serum creatinine level reduced to 310 µmol/L. Other blood parameters were within normal range. Renal ultrasound done was negative for obstruction.

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JCTN (2022) Volume 1: Article no: 2

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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After a month of follow-up, his blood urea nitrogen was 8 mmol/L and serum creatinine of 290 µmol/. Repeat urine analysis was negative for protein, glucose or blood. Twenty-four hours urine protein reading was 0.25 gram. Further tests ruled out other causes of acute kidney injury. Autoimmune screening done showed normal C3 and C4, negative anti neutrophilic antibody (ANA), antineutrophilic cytoplasmic antibody (ANCA) panel and anti-glomerular basement membrane (anti-GBM). Uric acid, lactate dehydrogenase and iron studies were within normal range. Hepatitis panel and HIV tests were negative. A few weeks later, he developed nausea, vomiting and lethargy and was admitted to the hospital. He did not have any symptoms suggestive of infection. His vital signs were within normal range; however he looked pale and dehydrated. His laboratory tests now showed blood urea nitrogen of 25.4 mmol/l, serum creatinine of 836 µmol/l and haemoglobin 7.7 g/dL. He had metabolic acidosis with pH of 7.28 and bicarbonate of 17 mmol/l. Urine analysis sent had no traces of protein, red cells or white cells. Repeated renal ultrasound showed normal size kidneys without obstruction or stones.

He was started on intravenous hydration and hemodialysis was initiated the subsequent day as his renal function deteriorated.

A renal biopsy was done and showed the presence of 20-30% intratubular oxalate cystals, strongly birefringent under polarized light (Fig.1). There was also presence of tubular atrophy and interstitial nephritis with lymphoplasmacytic cells and eosinophils. Tubular atrophy and interstitial fibrosis were estimated at 35-40% (Fig. 2,3). These findings were consistent with acute oxalate nephropathy.

The findings on renal biopsy triggered a deeper dietary and medication history. He was on multiple types of supplements for several years and had sought for a traditional healer to improve his general health. He stopped taking animal protein and only took plant-based, high anti-oxidants meals. This included a glass of spinach juice with a handful of almonds and cashew nuts daily. He was given Vitamin C tablets 3000 mg daily amongst other supplements, both in liquid and tablet form also containing vitamin C and other minerals. All in, the amount of Vitamin C taken from the supplements was amounting up to 6000 mg daily. He was on this exclusion diet for 2 weeks.

He was treated as acute kidney injury (AKI) with acute tubular necrosis (ATN) due to oxalate nephropathy secondary to oxalate rich diet. He was advised on a low oxalate diet and to stop all the supplements. ~~Urine for 24-hour oxalate was normal.~~

As his renal biopsy reported to have features of acute interstitial nephritis (AIN), he was started on oral prednisolone 60 mg daily, tapered over a period of 4 weeks. After a few sessions of hemodialysis and strict low oxalate diet, his serum creatinine levels slowly improved. Urine for 24- hour oxalate sent one month after the ordeal was within normal range at 263 umol/day. He was then monitored in clinic. However, during clinic follow up, his serum creatinine level was creeping up gradually and by the third month his it has peaked up to 980 µmol/L with blood urea nitrogen of 29 mmol/l. He was commenced on hemodialysis.

DISCUSSION

Oxalate nephropathy is characterized by deposition of calcium oxalate crystals within the renal tubules resulting in acute and chronic tubular necrosis, interstitial fibrosis and progressive renal insufficiency. Oxalate nephropathy can be either primary or secondary (1). Primary hyperoxaluria is an autosomal recessive enzymatic deficiency that leads to increased urinary excretion of oxalate (1). In contrast, secondary hyperoxaluria occurs either due to increased dietary ingestion of oxalate or oxalate precursor (such as ethylene glycol or vitamin C), fat malabsorption from various causes (Roux-en-Y gastric bypass surgery, chronic pancreatitis and use of Orlistat) and alteration in intestinal microflora resulting in increased oxalate absorption (1).

Oxalate can be found in many foods, including peanuts, rhubarb, spinach and sweet potatoes. Intake of vitamin C rich diet or supplements has also been associated with the formation of oxalate. Recent research has indicated that with even low levels of dietary vitamin C consumption, small increases in intake (> 281 mg/day vs < 105 mg/day) in male health professionals increased kidney stone risk by 31% (2).

Several case reports have been published linking the use of vitamin C and the development of oxalate nephropathy. K. Wong et al. reported a patient with metastatic carcinoma of the prostate with underlying obstructive renal insufficiency (3). The patient received a 60,000 mg bolus of IV vitamin C as an alternative therapy and subsequently developed anuric renal failure. Renal biopsy showed oxalate nephropathy. Few cases reported excessive consumption of cashew nuts, spinach and peanuts leading to oxalate nephropathy (4-5).

Our case differs from the other reported cases as it involved oral ingestion of high dose vitamin C. The patient consumed various foods high in oxalate and multiple supplements high in vitamin C (up to 6000mg daily), above the recommended daily intake of 65-90 mg daily. Comparing with the other reports, the development of

oxalate nephropathy is not dose-dependent. Our patient's risk factors for worsening kidney function were prolonged use of supplements and recent history of AKI. He did not have any genetic conditions, bowel diseases or prior history of kidney stones.

The clinical presentation of oxalate nephropathy varies and relates more to acute kidney injury. The diagnosis is confirmed by kidney biopsy showing tubular oxalate crystals. Cases in the literature have noted various degrees of complete recovery, partial recovery and end-stage renal disease requiring life-long dialysis.

As the incidence of diet-induced oxalate nephropathy is low, specific treatment guidelines do not exist. The recommended management is a low oxalate diet, high fluid intake, and the use of calcium carbonate to bind oxalate and potassium citrate for correction of metabolic acidosis. Steroids may be given to treat the inflammatory component of calcium oxalate deposition with subsequent improvement of kidney function.

CONCLUSION

Secondary oxalate nephropathy is rare but could lead to potentially devastating condition. This case highlights the potential danger of supplementation when one doesn't fully understand the subsequent impacts on the body; it also highlights the importance of dietary history when assessing someone's health, including a diet that is too exclusive or laden with potentially harmful substances. Vitamin C taken at high doses can induce hyperoxaluric nephropathy and progressive renal failure. Renal replacement therapy is required in more than 50% of the patients studied and most patients remain dialysis-dependent.

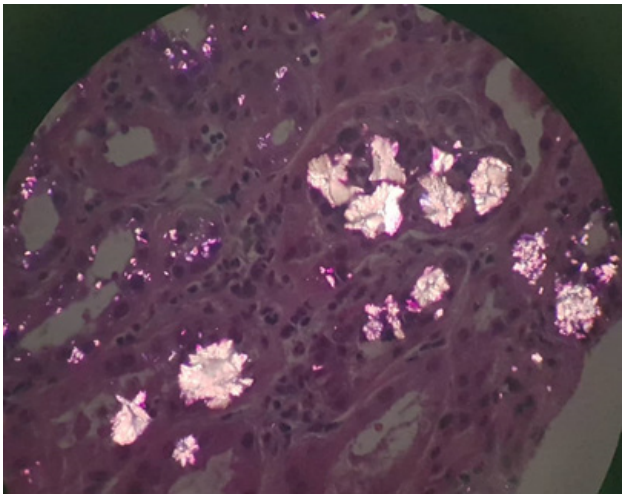

Fig. 1 Renal biopsy showing presence of intratubular oxalate crystals strongly birefringent under polarized light.

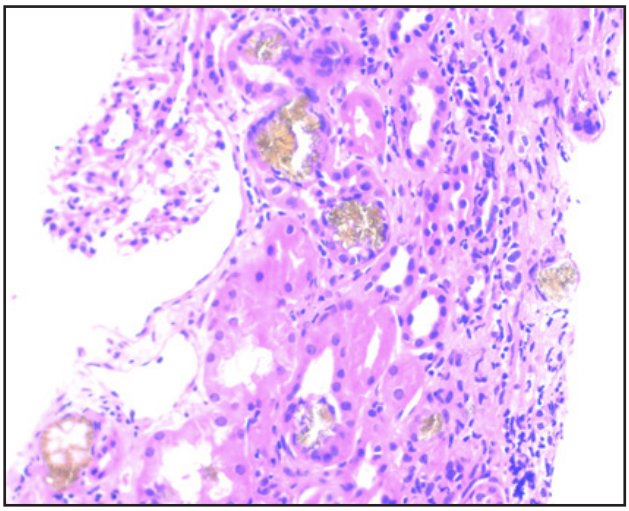

Fig. 2 Renal biopsy showing presence of tubular atrophy and interstitial nephritis (35-40%) with lymphoplasmacytic cells and eosinophils.

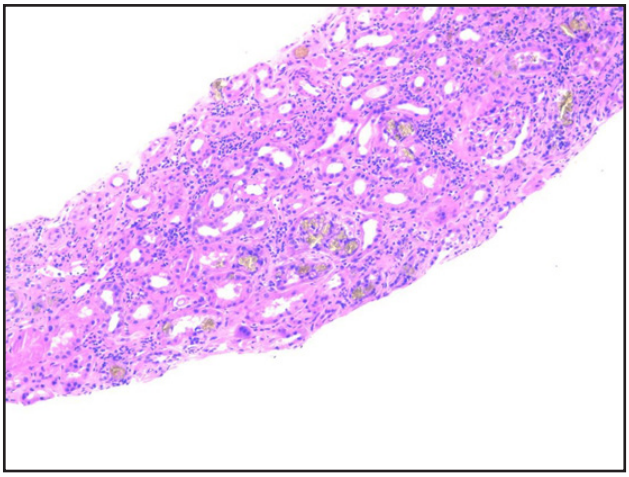

Fig.3 Renal biopsy showing presence of intratubular oxalate crystals with tubular atrophy and interstitial nephritis under H&E stain.

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Editorial

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SUCCESSFUL TREATMENT OF AN END-STAGE KIDNEY DISEASE PATIENT PRESENTING WITH SEVERE COVID-19 DISEASE USING ENHANCED CYTOKINE REMOVAL WITH HAEMOADSORPTION THERAPY IN ADDITION TO STANDARD MANAGEMENT

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ABSTRACT

End-stage kidney disease patients with severe COVID-19 disease have a higher mortality rate as compared to those with no comorbidities. Here we report a case of endstage renal disease patient on regular haemodialysis presenting with severe COVID-19 disease and subsequently developing septic shock during the inpatient stay. In addition to standard management with steroids because of the hypoxia, this patient also received antibiotics and haemoadsorption therapy to aid cytokine removal. There are limited data on the use of haemoadsorption in endstage renal disease patients with COVID-19 disease. This patient survived to discharge without the need for supplemental oxygen. In conclusion, combined therapeutic modalities are a possible promising treatment for severe COVID-19 infection in endstage renal disease patients.

Keywords: *COVID-19, End-stage kidney disease, haemoadsorption therapy*

INTRODUCTION

In December 2019, the novel coronavirus disease 2019 (COVID-19), emerged in China and spread across the world.[1] Patient may present with a range of symptoms such as fever, cough and fatigue but elderly patients and those with comorbidities are at a higher risk for severe forms of the disease.[1] Extracorporeal blood purification has been proven to effectively remove the released inflammatory cytokines in various conditions with hyper inflammation, hemophagocytic lymphohistiocytosis, intoxication, sepsis, and others.[2] Here we report the case of a patient with COVID-19 who benefited from haemoadsorption (HA). HA 330 cartridges contain neutro-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymer and these cartridges can remove cytokines, complements, free haemoglobin thus improving oxygenation and attenuating lung injury.[3] The recommended treatment duration is 2 to 2.5 hours but treatment duration can be prolonged depending on other hybrid therapies.[3]

CASE REPORT AND PRESENTATION

A 41-years old male with end-stage kidney disease (ESKD) on regular haemodialysis (HD) for the past 5 years via right brachiocephalic fistula presented to the emergency department (ED) with a history of fever, cough and worsening shortness of breath. He developed symptoms of fever after his first dose of COVID-19 vaccination 15 days before presentation. His last HD was 3 days before the presentation. His nasal swab Polymerase Chain Reaction (PCR) for Severe Acute Respiratory Syndrome

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JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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Coronavirus 2 (SARS-CoV-2) was positive with a cycle threshold (CT) value of 17. He was a chronic smoker, obese (body weight 120kg), and had hypertension.

On presentation (Day 1 of hospitalization), he had an oxygen saturation of 30% on room air (RA), 60% on reservoir bag-mask (HFM) (15L) and 95% on High Flow Nasal Cannula Oxygen (HFNC) (60L). Figure 2A shows the patient's chest X-ray (CXR) on presentation to ED. He underwent urgent HD with ultrafiltration (UF) of 2.5 litres. Post HD, he was admitted to our nephrology ward for further management.

Laboratory results at the emergency department revealed Haemoglobin 11.8g/dL,

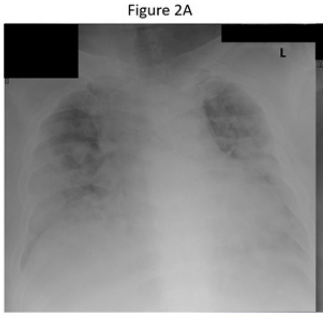
White Blood Count 13.45 x 10^3/µL with absolute neutrophil counts of 11.1 x 10^3/µL (normal range 2.0-7.0 x 10^3/µL) and lymphocyte counts of 1.2 x 103/µL (normal range 1.0-3.0x10^3/µL). His Sodium level was 124 mmol/L, Potassium 3.9 mmol/L, Urea 27.7 mmol/L, Creatinine 2,034 µmol/L, Alanine Aminotransferase (ALT) 101 U/L and Aspartate Aminotransferase (AST) 209 U/L (normal range 0-31). His creatine kinase (CK) level was 19,104 U/L, lactate dehydrogenase (LDH) 1,513 U/L with C-reactive protein (CRP) of 26.44 mg/dL. His recent Hepatitis B surface antigen and Anti HCV Antibodies tests were negative.

Table 1 summarises relevant laboratory tests on patient's initial presentation to the hospital and their reference range.

Test	On presentation	Reference Range
CRP, mg/dL	26.44	0-0.5, mg/dL
WBC, 10^3/µL	13.45	4.0-10.0, 10^3/µL
Hemoglobin, g/dL	11.8	13-17 g/dL
Platelets, 10^3/µL	181	150-410, 10^3/µL
Creatine Kinase, U/L	19,104	25-170, U/L
Lactate dehydrogenase, U/L	1,513	140-271, U/L
Procalcitonin, ng/mL	9.29	0-0.5 ng/mL
Urea, mmol/L	27.7	1.7-8.3, mmol/L
Creatinine, µmol/L	2,034	53-106, µmol/L
Albumin, g/L	42	35-50, g/L
Alanine Transaminase, U/L	101	0-43, U/L
Total Bilirubin, µmol/L	12	5-21, µmol/L

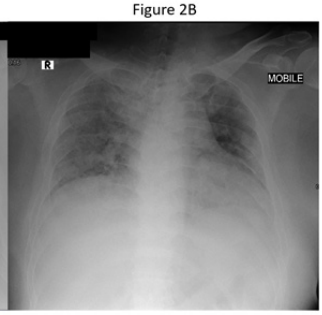
He was initiated on intravenous (IV) Dexamethasone 12mg once daily, oral pantoprazole and subcutaneous heparin for venous thromboembolism prophylaxis.

Figure 2A



CXR on Day 1 of hospitalization

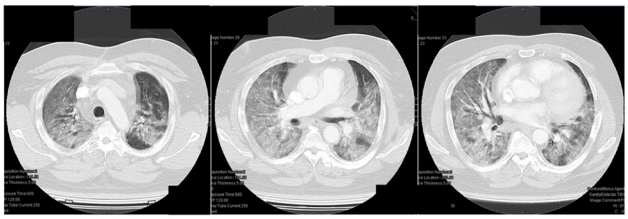
Figure 2B



CXR on Day 12 of hospitalization

His D dimer was positive hence a computed tomography pulmonary angiogram (CTPA) was done on day 3 of hospitalization which did not show any evidence of pulmonary embolism. The CTPA (Figure 3 images) showed ground glass densities with a crazy-paving pattern at the central and peripheral distribution of both lung fields. There was no pneumothorax or pneumomediastinum seen. Features in the lungs on the CTPA were consistent with severe COVID-19 infection with more than 75% lung involvement with organizing pneumonia.

Figure 3



CTPA on Day 3 of hospitalization

On day 5 of hospitalisation, his oxygen saturation worsened to 90% on 60L HFNC oxygen. He has initiated on IV Methylprednisolone 250mg once daily for 3 days. Despite the improvement in C-reactive protein levels (CRP) (see Table 2), his oxygenation requirements remained high and he was still dependent on High Flow Nasal Cannula 60L. Hence, on day 9 of hospitalization, he was treated with concomitant haemoadsorption (HA) therapy during his regular HD sessions with HA330 cartridge, Jafron Biomedical Co., Zhuhai, China. After one session of haemoadsorption therapy, oxygenation improved and he tolerated a face mask (FM) 8L/min with oxygen saturation of 98%. On room air, his oxygen saturation was 83%.

On day 12 of hospitalization, his oxygen saturation was 95% on nasal prong (NP) 3L/min. He developed hypotension with BP of 80/40 mmHg and heart rate of 115 bpm (regular). He was resuscitated with 500mls of 0.9%

JCTN (2022) Volume 1: Article no: 3

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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sodium chloride and repeated BP was 105/64 mmHg. A triple lumen catheter was inserted via the right femoral vein (ultrasound-guided). Blood cultures were obtained. He was treated with IV Cefepime and intravenous noradrenaline infusion. His dialysis therapy was modified to Sustained Low Efficiency Daily Dialysis (SLEDD) with concomitant haemoadsorption (HA).

Figure 2B shows his Chest X-ray post 2 sessions of haemoadsorption treatment.

On day 13 of hospitalization, he underwent another session of SLEDD with haemoadsorption.

The next day, his blood cultures grew gram-positive cocci and IV vancomycin was added. BP improved to 193/92 mmHg hence intravenous noradrenaline was discontinued. His oxygen saturation was 95% on NP 3L/min.

On day 19 of hospitalization, his oxygen saturation improved to 94% on room air. The blood cultures report was finalized showing mixed growth and he completed a total of 10 days IV cefepime and 8 days of IV Vancomycin. He was discharged home after 22 days of hospitalization with tapering dose of prednisolone and respiratory physician follow-up.

Table 2 summarises patient's progress and events during the course of his hospitalization.

Days of hospitalization	1	3	5	7
Oxygen saturation	30% on room air (RA), 60% on HFM 15L, 95% on HFNC 60L	96% on HFNC 60L	90% on HFNC 60L	95% on HFNC 60L
Steroid dose	IV Dexamethasone 12mg OD	IV Dexamethasone 12mg OD	IV Methylprednisolone 250mg OD	IV Methylprednisolone 250mg OD
HD/HA	HD UF 2.5L (done during early morning of Day 2)	-	HD UF 1.5L	HD UF 2L
Events	CXR	CTPA	-	-
Antibiotics	-	-	-	-
Laboratory Results	WCC 13.45 x 10^3/µL (Absolute lymphocyte 1.2) Hb 11.8 g/dL Platelets 181 ALT 101 U/L AST 209 U/L CK 19,104 U/L LDH 1,513 U/L CRP 26.44 mg/dL Urea 27.7 mmol/L Na 124 mmol/L K 3.9 mmol/L Creatinine 2034 µmol/L Albumin 42 g/L	D dimer positive 4.81 mcg/mL	WCC 9 x 10^3/µL Hb 11 g/dL Platelets 248 ALT 65.4 U/L CRP 7.15 mg/dL Urea 54.6 mmol/L Na 134 mmol/L K 4.4 mmol/L Creatinine 2223 µmol/L Albumin 34.8 g/L Procalcitonin 9.29 ng/mL	WCC 8.05 x 10^3/µL Hb 10.8 g/dL Platelets 303 ALT 144 U/L Urea 57.9 mmol/L Na 132 mmol/L K 4.6 mmol/L Creatinine 1925 µmol/L Albumin 34.9 g/L

Days of hospitalization	9	10	11
Oxygen saturation	98% on HFNC 60L	98% on FM 8L	92% on FM 5L, 83% on RA
Steroid dose	IV Dexamethasone 20mg OD	IV Dexamethasone 20mg OD	IV Dexamethasone 20mg OD
HD/HA	HD UF 1.5L + HA 330	-	-
Events	-	-	-
Antibiotics	-	-	-
Laboratory Results	WCC 7.68 x 10^3/µL Hb 10.7 g/dL Platelets 290 Urea 68.6 mmol/L Na 131 mmol/L K 5 mmol/L Creatinine 1786 µmol/L Albumin 33.3g/L		

JCTN (2022) Volume 1: Article no: 3

JOURNAL OF CLINICAL AND TRANSLATIONAL NEPHROLOGY (JCTN)

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Days of hospitalization	12	13	14
Oxygen saturation	95% on NP 3L	94% on NP 3L	95% on NP 3L
Steroid dose	IV Dexamethasone 16mg OD	IV Dexamethasone 16mg OD	IV Dexamethasone 16mg OD
HD/HA	SLEDD UF 1L +HA 330	SLEDD UF 1L + HA 330	-
Events	• CXR done • Hypotension- Fluid resuscitated • IV Noradrenaline infusion started via triple lumen inserted into right femoral vein	-	• Blood cultures grew gram positive cocci. • IV Noradrenaline infusion discontinued.
Antibiotics	IV Cefepime	IV Cefepime	IV Cefepime IV Vancomycin
Laboratory Results	WCC 44.67 x 10^3/µL Hb 10.5 g/dL Platelets 296 ALT 69 U/L CK 1305 U/L Urea 73.3 mmol/L Na 129 mmol/L K 5.8 mmol/L Creatinine 1305 µmol/L Albumin 30.1g/L	Procalcitonin 11.83 ng/mL	WCC 9.7 x 10^3/µL Hb 9.2 g/dL Platelets 202 ALT 42.3 U/L CK 244 U/L CRP 24.62 mg/dL

Days of hospitalization	15	16	19
Oxygen saturation	96% on NP 3L, 92% on RA	94% on NP 3L, 81% on RA	94% on RA
Steroid dose	Prednisolone 60mg OD	Prednisolone 60mg OD	Prednisolone 55mg OD
HD/HA	-	HD UF 3L	HD UF 3.5L
Events	-		
Antibiotics	IV Cefepime IV Vancomycin	IV Cefepime IV Vancomycin	IV Cefepime IV Vancomycin
Laboratory Results		WCC 9.92 x 10^3/µL Hb 8.5 g/dL Platelets 185 ALT 31.6 U/L Urea 66.8 mmol/L Na 132 mmol/L K 6.0 mmol/L Creatinine 1356 µmol/L Albumin 31.4g/L	WCC 17.2 x 10^3/µL Hb 8.7 g/dL Platelets 139 ALT 50.6 U/L CRP 1.54 mg/dL Urea 71.9 mmol/L Na 130 mmol/L K 5.7 mmol/L Creatinine 1354 µmol/L Albumin 32.3g/L

Days of hospitalization	20	21	22
Oxygen saturation	90% on RA		94% on RA
Steroid dose	Prednisolone 55mg OD	Prednisolone 40mg OD	Prednisolone 40mg OD with tapering dose every 3 days
HD/HA		HD UF 2.5L	-
Events		USS Doppler and Dilution USS done – no recirculation	Discharged with respiratory physician followup as outpatient
Antibiotics	IV Cefepime IV Vancomycin	IV Cefepime IV Vancomycin	-
Laboratory Results	-	-	-

JCTN (2022) Volume 1: Article no: 3

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DISCUSSION

Amongst hospitalized patients with COVID-19, mortality risk was increased in patients with ESKD compared to that in the general population.[4] The mortality rates amongst endstage kidney disease patients on dialysis hospitalised for COVID-19 infection was reported to be between 13.3% to 42.1%.[4] In a cross-sectional study, it was noted that the mortality rate was significantly lower in patients who received haemoadsorption without having mechanical ventilation.[1] In those who required mechanical ventilation, the duration of mechanical ventilation was lower when haemoadsorption was initiated prior to needing mechanical ventilation.[1] Another promising finding was that the PaO2/FiO2 ratio significantly increased in all patients after hemoperfusion resulting in improvement in oxygenation.[1]

This patient's presentation was unusual as he had symptoms almost 14 days before presentation. His PCR test was positive 3 days prior to presentation. His condition was ill at presentation with severe hypoxia, raised inflammatory markers and elevated LDH and CRP levels. He was probably fluid overloaded as well having missed one session of his usual HD treatment. At presentation, this patient had liver injury (as documented by the raised liver enzymes and LDH levels) as well as probable skeletal muscle injury as documented by the elevated creatine kinase (CK) levels.

In an early study from Wuhan, skeletal muscle injury (defined as patient having skeletal muscle pain and elevated serum CK greater than 200 U/L) appears to be significantly more frequent in severe COVID-19 compared to less severe diseases (19.3% versus 4.8%).[5] The receptor angiotensin-converting enzyme 2 (ACE2) was identified as the functional receptor for SARS-CoV-2 and this receptor is present in multiple human organs including the skeletal muscles hence it has been postulated that myocytes are also susceptible to direct muscle invasion by SARS-CoV-2.[5]

For this patient, the use of steroids likely helped with the initial early phase of acute respiratory distress syndrome (ARDS) as the CRP level appears to improve. However, despite treatment with high dose steroids and haemodialysis with ultrafiltration, his oxygen requirement remained high and hence haemoadsorption treatment was added to his usual haemodialysis session. The patient subsequently developed septic shock due to bacterial infection on Day 12 of hospitalization and the haemoadsorption treatment during that period could have been beneficial. There was a gradual decline in haemoglobin levels and an increase in urea levels during his inpatient stay but there was no overt clinical evidence of gastrointestinal bleed. As this patient was admitted to the hospital during the peak of the pandemic and due to the limitation of services, he did not undergo further endoscopic examination given no clinical evidence of overt bleeding and he remained haemodynamically stable. An ultrasound doppler and ultrasound dilution test was done for the patient's fistula which did not show any recirculation hence the high urea was attributed to the high dose steroids used. This patient's Chest X-ray appeared to have improved slightly after the use of steroids, two applications of haemoadsorption therapy and a few haemodialysis sessions with ultrafiltration. He was discharged home well without the need for supplemental oxygen therapy.

CONCLUSION

The application of haemoadsorption therapy in addition to standard management in this patient may have been beneficial in terms of cytokine removal during sepsis. It is unclear whether the haemoabsorption prevented the progression of the disease to severe ARDS as he also had concomitant haemodialysis with ultrafiltration which may have improved his oxygenation. Ultimately, this patient did not require mechanical ventilation and was discharged home not requiring any supplemental oxygen therapy.

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