



WHAT DID WE LEARN ABOUT CORONAVIRUS DISEASE-19-ASSOCIATED ACUTE KIDNEY INJURY DURING THE PANDEMIC?

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ABSTRACT

Initial reports suggested that kidney involvement after coronavirus disease 19 (COVID-19) infection was uncommon, but this premise appears to be incorrect. Acute kidney injury can occur through various mechanisms and complicate the course of up to 25% of patients with COVID-19 hospitalized in our Institution, and of over 50% of those on invasive mechanical ventilation. Mechanisms of injury include direct kidney injury and predominantly tubular, although glomerular injury has been reported, and resulting from severe hypoxic respiratory failure, secondary infection, and exposure to nephrotoxic drugs. The mainstay of treatment remains the prevention of progressive kidney damage and, in some cases, the use of renal replacement therapy. Although the use of blood purification techniques has been proposed as a potential treatment, results to date have not been conclusive. In this manuscript, the mechanisms of kidney injury by COVID-19, risk factors, and the mainstays of treatment are reviewed. (REV INVEST CLIN. 2022;74(6):287-301)

Keywords: Acute kidney injury. Coronavirus disease 19. Renal replacement therapy. Blood purification techniques. Cytokines.

INTRODUCTION

In March 2020, the World Health Organization declared the novel coronavirus disease (COVID-19) a global pandemic¹. The presentation of COVID-19 varies considerably and includes asymptomatic individuals, patients with mild respiratory symptoms, and the more severe disease spectrum in patients requiring

hospitalization. The most severe cases are complicated by multiple organ dysfunction syndrome (MODS), with the kidney being one of the most affected organs, and reflecting the entire spectrum of acute kidney injury (AKI)^{2,3}. We, herein, focus on describing all aspects of COVID-19-associated AKI (C19-AKI), including its epidemiology, proposed pathogenesis, management, and long-term outcomes.

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EPIDEMIOLOGY OF C19-AKI

Initial reports suggested that AKI, as defined by the kidney disease improving global outcomes (KDIGO) criteria⁴, was uncommon following acute COVID-19 infection. Subsequent observations showed that C19-AKI occurs in 20% to 50% of hospitalized cases, with variations per institution, and with a decreasing trend in its incidence as the pandemic has evolved^{5,6}. AKI rates are higher than those observed in the Influenza H1N1 pandemic and other illnesses, suggesting a kidney-specific susceptibility to this infection⁷.

AKI studies have classified it according to the site of acquisition, whether detected in the community on patient admission, or if it develops during hospitalization. This is relevant given the different characteristics of these patients⁸. In Mexican patients with SARS-CoV-2 infection who developed AKI, approximately two-thirds of AKI were community-acquired C19-AKI, and one-third was hospital-acquired C19-AKI, and both scenarios led to a dismal prognosis⁸.

As expected, rates of C19-AKI are higher in patients admitted to an intensive care unit (ICU), with reported incidences of 50-90%, and mostly in patients on invasive mechanical ventilation (IMV)⁹. In this context, 30-60% of C19-AKI are detected in severe AKI stages (Stages 2 and 3 of the KDIGO classification), and 6% to 39% require organ support with renal replacement therapy (RRT)^{10,11}.

As in other diseases, the development of AKI is a poor prognostic factor. C19-AKI has been associated with higher in-hospital mortality rates (C19-AKI stages 1-3, HR = 5.6 [95% CI: 5.0-6.3], and C19-AKI with RRT (HR = 11.3 [95% CI: 9.6-13.1]), longer hospitalizations (patients with C19-AKI, 11.6 [IQR: 6.9-20.9] days versus patients without AKI, 5.2 [IQR: 3.0-8.6] days)^{11,12}), and an increased risk of developing chronic kidney disease (CKD) in survivors at 3 months; 16% of all AKI survivors had CKD^{12,13}.

RISK FACTORS FOR C19-AKI

There are many risk factors linked with the development of C19-AKI in clinical studies that vary depending on the population selection, differences in AKI prevalence, the AKI criteria applied, and the timing of

hospital admission, among others. For example, C19-AKI is more commonly reported in studies conducted in countries other than China, or when based on a prospective clinical design instead of a retrospective analysis¹⁴. However, despite the heterogeneity of clinical studies, the most consistent risk factors found to be strongly associated to the development of C19-AKI are COVID-19 severity, older age, male sex, and a previous CKD diagnosis (Table 1).

Undoubtedly, the key factor for C19-AKI is the severity of COVID-19¹⁴. Severe COVID-19 is directly associated with ICU admission, the development of acute respiratory distress syndrome (ARDS), IMV, the use of vasopressors, and MODS; all are strongly linked with the development of C19-AKI¹⁵. Likewise, many surrogates of severe inflammation caused by COVID-19 such as high levels of ferritin, D-dimer, lactate dehydrogenase, IL-6, or creatine kinase have been associated with C19-AKI⁸. The risk of C19-AKI in symptomatically mild COVID-19 seems odd, but there are case series reports of patients with mild COVID-19 and severe kidney dysfunction and/or heavy proteinuria^{15,16}. The risk factors for C19-AKI identified in this population are the same as those reported in patients with severe COVID-19, such as male sex, older age, obesity, hypertension, diabetes, and pre-existing CKD, among others¹⁵. In several series, cases of severe AKI and proteinuria in patients with mild COVID-19 have been identified in three contexts: relapses of previous glomerular disease, *de novo* glomerulopathies, and those associated with SARS-CoV-2 vaccination. These populations harbor risk factors such as pre-existing kidney disease, high-risk APOL1 genotypes, molecular mimicry of an antigen in individuals with an underlying genetic susceptibility, or specific HLA haplotypes^{16,17}.

In contrast, interventions that decrease the risk of severe COVID-19 such as vaccination or dexamethasone administration effectively decrease the number of C19-AKI cases¹⁸. These “protective factors” could possibly explain the declining rates of C19-AKI throughout the pandemic¹⁹. Another possible, but rarely mentioned risk factor for C19-AKI, is the virulence of the variant sub-type of the SARS-CoV-2 virus. Studies have indicated that the risk posed by the omicron variant (B.1.1.529) in terms of hospitalization is lower than that of the delta variant (B.1.617.2)²⁰. It is plausible that the decreased

Table 1. Risk factors associated with C19-AKI (adapted from Cai et al.¹⁴ and Raina et al.¹⁵)

Risk factor	Association strength
Non-modifiable risk factor	
Elderly	OR = 3.94 (95% CI: 1.55–9.99) for age \geq 60 years
Male sex	OR = 1.37 (95% CI: 1.25–1.49)
Non-Asian	OR = 2.34 (95% CI: 1.50–3.64)
Risk factors related to baseline health status	
Previous CKD	OR = 4.56 (95% CI: 3.63–5.73)
CAD	OR = 1.98 (1.74–2.24)
Hypertension	OR = 1.85 (95% CI: 1.70–2.02)
DM	OR = 1.71 (95% CI: 1.59–1.84)
Lung disease	OR = 1.36 (95% CI: 1.16–1.60)
Cancer	OR = 1.26 (95% CI: 1.13–1.40)
Risk factors related to severe COVID-19	
Mechanical ventilation	OR = 8.61 (95% CI: 5.63–13.17)
Use of vasopressors	OR = 8.33 (95% CI: 4.72–14.72)
Risk factors, potentially modifiable	
Smoking	OR = 1.23 (95% CI: 1.07–1.42)
BMI $>$ 30 kg/m ²	OR = 1.12 (95% CI: 1.01–1.25) Borderline risk, in a few cohorts the association is only observed when BMI $>$ 35 kg/m ²

OR: odds ratio; cardiovascular disease (CAD): coronary artery disease and heart failure; DM: diabetes mellitus; BMI: body mass index.

severity of COVID-19 due to the omicron variant translates into a lower rate of C19-AKI. Other risk factors are shown in table 1.

However, many risk factors remain inconclusive. Transplantation is considered a potential risk factor for AKI in many infectious diseases, given the high prevalence of pre-existing limited graft function and comorbidities, and the possible detrimental effects of immunosuppressive drugs in kidney transplant recipients (KTR)²¹. In a recent systematic review of 5,559 KTR, the risk of C19-AKI was higher in these patients compared with non-transplanted patients, regardless of sex, age, and comorbidities²². Even so, less biased larger studies revealed a similar rate of AKI in KTR in comparison with non-transplanted COVID-19 patients²². Given the broad heterogeneity of KTR characteristics, adjusting the effect for important confounders is difficult to achieve.

The use of certain medications before hospital admission may be a relevant risk factor for COVID-19

outcomes. Several meta-analyses have demonstrated that the use of renin-angiotensin-aldosterone system inhibitors (RAASis) does not have a detrimental effect on the clinical course of SARS-CoV-2 infection^{23,24}. In a systematic review, a medical history of RAASI use in hospitalized patients was associated with a moderate to a severe increase in the risk of C19-AKI (OR = 1.68, 95% CI: 1.19–2.36); however, only retrospective studies were included in this review²⁵. Contrarily, a randomized controlled trial found that the risk of severe AKI requiring hemodialysis was not different in COVID-19 hospitalized subjects who continued receiving RAASI compared with those who discontinued the medication²⁶.

Other “prognostic” factors associated with the course and outcome of renal injury are rarely reported. Risk factors should be reported, as recommended, according to the biphasic pattern of C19-AKI: “early” AKI (AKI manifested at hospital admission) and “delayed” AKI (AKI developed during hospitalization)⁸. Further, there is a need to recognize and identify modifiable and preventable C19-AKI risk factors.

PATHOPHYSIOLOGY OF C19-AKI

The pathophysiological mechanisms of C19-AKI are multifactorial and include systemic immune and inflammatory responses induced by the viral infection, endothelial injury, and direct epithelial infection². Furthermore, patients with COVID-19 usually present with volume depletion resulting from fever, shortness of breath, and gastrointestinal losses (Fig. 1)²⁷. These findings are summarized in the following subsections.

Viral tropism for the kidney

The SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) receptor as a gateway to infect human cells²⁸. ACE2 RNA is expressed in multiple organs, such as the lung, intestines, and kidney. However, ACE2 expression is greater in the kidney than in the lung; the main cells expressing this enzyme in the kidney are podocytes and proximal tubular epithelial cells and are, hence, more susceptible to infection and subsequent injury^{27,29-31}.

Most ACE2 is present in insoluble form and bound to cell membranes. ACE2, in both the soluble and insoluble forms, converts angiotensin II to angiotensin (1–7), which is crucial to the control of different functions in the body^{2,28}. The SARS-CoV-2 viral spike glycoprotein also binds with high affinity to ACE2, triggering its internalization along with the virus^{28,31}. Intracellular translocation of SARS-CoV-2 and ACE2 leads to its depletion, loss of its normal endogenous enzyme function, and concomitant depletion of its catalytic product, Ang (1-7), thus hindering its vasodilatory effects, antiproliferative, and antifibrotic functions^{32,33}.

Although these are possible explanations, there is no convincing evidence of direct SARS-CoV-2 renal tropism. Few studies have been able to demonstrate the presence of viral particles in renal tissue, and many have failed to do so^{16,34,35}. These discrepancies could result from the time lapse between infection and biopsy procurement, the severity of the condition, and the samples' processing techniques³⁶. On the other hand, various reports documenting SARS-CoV-2 virions or virus-like particles also describe physiological structures and organelles, such as clathrin-coated vesicles, multi-vesicular bodies, rough endoplasmic reticulum, and unidentified subcellular structures. This problem results primarily from the techniques used in its detection³⁷.

Tubular and glomerular injury

Kidney injury caused by COVID-19 typically manifests as tubular damage with urinalysis abnormalities (low-grade proteinuria, hematuria, and/or impaired glomerular filtration rates)³⁸. Renal biopsies and post-mortem studies frequently document acute tubular injury by light microscopy, and in some reports, viral particles have been detected within renal tubular epithelial cells and podocytes by electron microscopy³⁹. This last finding has been debated since they have not been documented in all biopsies, perhaps as a result of the processing technique, the severity of the disease, and the time lapse between infection and sample collection.

Many studies have reported patients with COVID-19 and a collapsing glomerular disease^{40,41}. The two possible underlying mechanisms could be cytokine-mediated injury to podocytes and/or direct toxic viral effects on podocytes. Genetic susceptibility, especially the presence of high-risk apolipoprotein 1 (APOL1) genotypes, may play a key role in its pathogenesis^{40,41}. Other *de novo* glomerulopathies or relapses of a previous disease have been subsequently reported^{42,43}.

Complement activation

The complement system, a significant component of native immunity, is critical to the rapid response against infections. Due to its central role in the detection and removal of pathogens, complement should intuitively be protective in SARS-CoV-2 infection⁴⁴. SARS-CoV-2 *per se* can activate the complement system directly through the lectin pathway, the classical pathway, and/or the alternative pathway^{45,46}. Specifically, the spike and nucleocapsid proteins of SARS-CoV-2 can be directly recognized through the lectin pathway; IgG and IgM antibodies directed against the receptor-binding domain within the spike protein initiate activation of the classical pathway, and the SARS-CoV-2 spike protein can directly dysregulate the alternative complement activation pathway by binding to heparan sulfate and competing with factor H^{47,48}.

Multiple lines of evidence implicate hyperactivation of the complement system in the pathophysiology of COVID-19. How and why the normally protective complement system becomes pathogenic in COVID-19

remains unknown^{44,45}. Complement activation has been demonstrated in the kidney, with evidence of complement factor deposition and of the membrane attack complex in nephron vessels and on the tubular basement membrane⁴⁶. These findings have led to studies on the effects of the complement C5a inhibitor, eculizumab, in COVID-19 patients; although preliminary results appear promising, these studies have not reached a sufficient number of patients to demonstrate any significant effects on C19-AKI⁴⁹.

Cytokine activation

SARS-CoV-2 binding to ACE-2 receptors and viral replication in lung cells lead to epithelial and endothelial cell apoptosis and vascular leakage and promote the activation of the inflammatory cascade². These inflammatory cytokines and chemokines then recruit more innate immune cells and activate adaptive immune cells to sustainably release more inflammatory cytokines that further aggravate the injury⁵⁰.

Many studies have shown that COVID-19 patients have elevated levels of numerous inflammatory cytokines, including IL-1 β , IL-2, IL-6, IL-10, IFN- γ , and TNF- α , and that these cytokines correlate with disease severity and outcomes⁵¹. Th17 cells have both a protective and a pathogenic role in COVID-19; they play an important role in its pathogenesis, not only activating the cytokine cascade but also inducing Th2 responses that inhibit Th1 differentiation and suppress Treg cells⁵².

Targeted immunomodulation in the management of COVID-19 infection (e.g., tocilizumab) and non-specific immunosuppression (e.g., corticosteroids) can be used to limit the collateral damage caused by the adversely activated immune system. Pharmacological treatments and extracorporeal blood purification therapies have been tested in an attempt to decrease circulating interleukin levels (IFN- γ , IL-16, and IL-10); however, this decrease in cytokines has not translated into an improvement in mortality⁵³⁻⁵⁵.

On the other hand, some observational studies have described that low levels of IL-4, IL-17, and IFN- γ herald a worse prognosis, but these results are controversial, because they depend on the timing of the sample collection, the site of procurement (BAL vs. serum), and its subsequent processing⁵⁶.

COVID-19-associated coagulopathy

Endothelial cells contribute to the preservation of normal hemostasis by maintaining vessel wall integrity and balancing fibrinolysis through the expression of coagulation inhibitors and blood clotting enzymes⁵⁷. SARS-CoV-2 may alter vascular homeostasis by directly infecting endothelial cells through ACE2. Furthermore, a decrease in ACE2 expression might, in turn, indirectly activate the kallikrein-kinin system, ultimately leading to increased vascular permeability². Pro-inflammatory cytokines can also induce a capillary leak syndrome and thrombosis, which may result in disseminated intravascular coagulation^{2,27}. The main hematological abnormalities reported in these patients consisted of leukopenia, lymphopenia, anemia, and thrombocytopenia, and the proportion of their decrease was usually a harbinger of disease progression and severity^{58,59}.

The prothrombotic nature of COVID-19-associated sepsis has been well described. Platelet-rich thrombi have been observed in the microvasculature of the heart, brain, kidney, and liver; renal infarctions secondary to arterial thrombi have also been described, especially in the early phases of the pandemic⁵⁷.

Indirect kidney injury

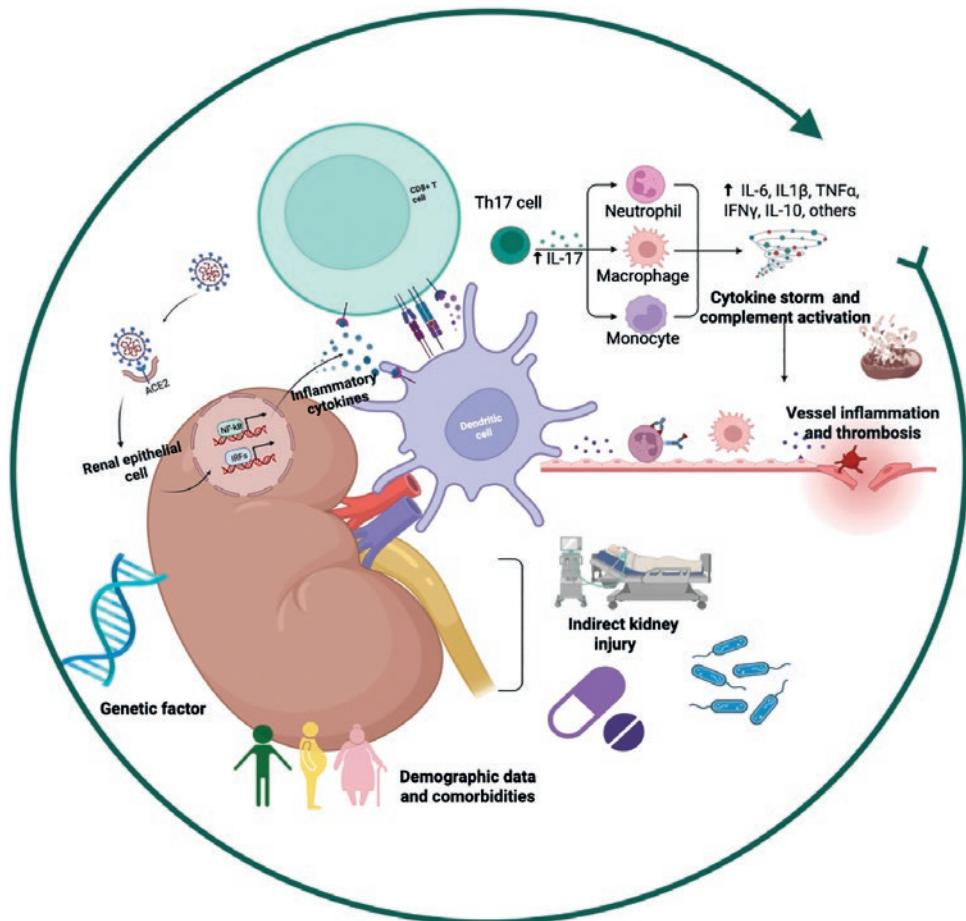
Several non-specific mechanisms may contribute to the development of C19-AKI, including hemodynamic abnormalities, cardiac dysfunction, hypovolemia due to poor oral intake or high fever, the use of nephrotoxic drugs (antibiotics or contrast medium), and hospital-acquired sepsis⁵⁷. Furthermore, the high positive-pressure levels used in IMV can potentially induce or exacerbate abnormalities in intrarenal blood flow and promote other hemodynamic changes that impair renal perfusion^{2,57}. All these direct and indirect mechanisms, some of them speculative, contribute to the development of C19-AKI (Fig. 1).

C19-AKI: RECOGNITION

Early diagnosis of AKI was a challenge during the COVID-19 pandemic and in every discipline of healthcare. In Mexico, renal involvement at hospital admission was more prevalent in older patients⁸,

Figure 1. Pathophysiological mechanisms of C19-AKI.

The pathophysiological mechanisms of C19-AKI are multifactorial and include systemic immune and inflammatory responses induced by viral infection, endothelial injury, and direct epithelial infection. On the other hand, several non-specific mechanisms may contribute to the development of C19-AKI, including hemodynamic abnormalities, hypovolemia from poor oral intake or high fever, use of nephrotoxic drugs, and hospital-acquired sepsis. Risk factors for C19-AKI, sex, age, and hereditary susceptibility, are of relevance in the pathogenesis.



and in those with a history or associated comorbidities (hypertension, CKD, and obesity), conditions characteristically associated with decreased renal reserves^{8,60,61}.

The precise etiology of C19-AKI in different cohorts, including Mexican cohorts, cannot yet be fully elucidated, and given the diversity in its presentation; in many cases, the etiology is multifactorial. However, sepsis and hemodynamic instability may play a predominant role in these cases^{5,8}. The timing between the initial development of AKI and hospital admission varies between cohorts. In a multicentric study, Hirsch et al.⁵ described that most cases developed early, with 37.3% of cases manifesting AKI at admission or

developing it within 24 h of admission; they also observed a significant relationship between the presence of respiratory failure and AKI, unmistakable manifestations of the inflammatory phase of the disease^{5,61}.

In 2020, the 25th Consensus Conference of the acute disease quality initiative (ADQI) focused on this new disease³. They recommended the use of the KDIGO criteria to define and report C19-AKI and thus enable reproducibility in study comparisons, and improve survival with the increased and timely recognition of this entity⁴. Traditionally, an AKI diagnosis is based on changes in kidney function such as increased serum creatinine (sCr), which is a low sensitivity method

since nearly 50% of the glomerular filtration rate (GFR) must be lost before a change in sCr is detectable, and decreased urine output, which lacks specificity since it may be triggered by hypovolemia and totally unrelated with kidney injury³.

The severity of C19-AKI may be classified with the well-documented consensus KDIGO criteria for AKI staging, and outcomes appear to correlate with the severity of AKI as defined by this classification system⁴. As mentioned above, the severity of C19-AKI may lead to different outcomes. In addition, the concept of the duration of AKI should also be considered in the description of AKI, as recently described in a prospective cohort by Casas et al., in which persistent AKI was also associated with increased mortality (HR = 7.42, 95% CI: 1.04-53.04, p = 0.046)⁶².

Additional tools may be useful to confirm or support a C19-AKI diagnosis and to establish differential diagnoses and prognostic assessments⁴. Urinalysis and urine chemistries such as urinary sodium (UNa) levels, fractional excretion of sodium (FeNa), and fractional excretion of urea (FeU) are commonly used to differentiate pre-renal AKI from acute tubular necrosis (ATN), but they remain insensitive and non-specific markers, offering little reliable information to establish a diagnosis of AKI. Martínez et al.⁸, analyzed the urinalyses and urine electrolytes of patients with community-acquired and hospital-acquired C19-AKI, and they reported a high prevalence of FeNa < 0.5% (71 vs. 71%), a similar proportion of cases with proteinuria > 2+ (34 vs. 41%), but a higher proportion of hematuria in patients with hospital-acquired C19-AKI (59 vs. 28%). These findings are in line with a study reported by Morita et al.⁶³, in which the urinary sediment findings in subjects with COVID-19 were more severe as renal function declined. These two cohorts suggest that glomerular hypoperfusion might be largely involved in the pathogenesis of C19-AKI and at least partially conserved tubular sodium absorption, without a full-blown classic acute tubular injury presentation^{8,63}. Thus, the use of these markers in C19-AKI appears to be even more limited since C19-AKI has a complex pathophysiology that affects more functions other than tubular reabsorption.

Biomarkers can help to differentiate various types of kidney injury and may be uniquely helpful in quantifying tubular injury in COVID-19 and predicting

progression of AKI stage, the need for RRT, or death⁶². The elevation of kidney injury urinary biomarkers in the absence of changes in sCr and a normal urine output have been considered subclinical AKI, a term identifying those patients at high risk of AKI. These patients are likely to benefit from obtaining biomarkers and performing early interventions. In this context, the tissue inhibitor of metalloproteinases-2 (TIMP-2) and the insulin-like growth factor binding protein-7 (IGFBP7) have been identified as possible AKI biomarkers, given that both are released following ischemic or inflammatory processes in the kidney, resulting in transient G1 cell cycle arrest⁶⁴. Another biomarker of early AKI is the urinary neutrophil gelatinase-associated lipocalin (NGAL); the intrarenal concentration of this protein is abruptly up-regulated soon after ischemic or nephrotoxic kidney injury⁶⁴. A recent Mexican cohort study of critically ill patients with SARS-CoV-2 infection and without functional criteria of AKI established that the result of the formula $(\text{TIMP-2}) \times (\text{IGFBP7}) > 0.2 \text{ (ng/mL)}^2/1000$ was associated with AKI during hospitalization (HR = 7.23 [0.99-52.4], p = 0.050)⁶². These biomarkers, in conjunction with clinical findings, were useful to identify subclinical AKI in critically ill COVID-19 patients. Table 2 summarizes the different urinary biomarkers used in hospitalized patients with C19-AKI^{62,65-71}.

MANAGEMENT OF C19-AKI

According to the KDIGO guidelines, the management of patients with C19-AKI should not differ from that of patients with AKI due to other causes⁴. However, there are some particularities in COVID-19 that should be considered (Fig. 2).

Optimal fluid management is essential. In C19-AKI, we have seen dynamic courses in which hypovolemia secondary to fever, cough, diarrhea, anorexia, and hypercatabolism can develop during early infection. Once hospitalized, some patients require intubation, which further promotes volume depletion. Appropriate fluid resuscitation and avoiding fluid overload are essential steps at this stage, and balanced crystalloids should be considered as first-line treatment⁷². On the other hand, during hospitalization, it is not uncommon that patients become fluid overloaded⁷². Therefore, objective and dynamic evaluation of intravascular volume and heart and lung status with conventional

Table 2. Urinary biomarkers in hospitalized patients with C19-AKI^{62, 65-71}

Biomarkers	Author	AUC (95% CI)	Sensitivity	Specificity	Observations
Injury Biomarkers					
uNGAL	Xu et al. ⁶⁵				n = 444
	AKI 2-3	0.83 (0.77–0.89)	0.89	0.67	Cutoff 200 ng/mL
	RRT	NR	0.84	0.63	
	Pode et al. ⁶⁶				n = 52
	AKI	0.81 (0.68–0.95)	0.64	0.93	Cutoff 120 ng/L
	RRT	0.87 (0.75–1.00)	0.75	0.93	Cutoff 190 ng/L
	Casas et al. ⁶²				n = 51
	AKI	0.70 (0.55–0.85)	0.54	0.76	Cutoff 45 ng/mL
	He et al. ⁶⁷				n = 174
	AKI	0.82 (0.82–0.96)	0.80	0.92	
	Vogel et al. ⁶⁸				n = 80
	AKI	0.69	NR	NR	
	Menez, et al. ⁶⁹				n = 153
	Composite: AKI-3, RRT, death within 60 days	NR	NR	NR	HR = 1.34 (95% CI: 1.09-1.84)
uKIM-1	Xu et al. ⁶⁵				n = 444
	AKIN 2-3	0.58 (0.50–0.67)	NR	NR	Cutoff 200 ng/mL
	Vogel et al. ⁶⁸				n = 80
	AKI	0.81 (NR)	0.87	0.65	
	Menez, et al. ⁶⁹				n = 153
	Composite: AKI-3, RRT, death within 60 days	NR	NR	NR	HR = 2.03 (95% CI: 1.38-2.99)
Cell-Cycle Arrest Biomarkers					
TIMP-2/IGFBP7	Casas et al. ⁶²				n = 51
	AKI	0.68 (0.53–0.82)	0.40	0.88	0.2 ng/mL ² /1000
	Panga et al. ⁷⁰				n = 81
	AKI 1-3	0.62 (0.38–0.87)	0.57	0.74	0.59 ng/mL ² /1000
	AKI 2-3	0.78 (0.51–1.0)	NR	NR	0.29 ng/mL ² /1000
Functional Biomarker					
Cystatin C	Pode et al. ⁶⁶				n = 52
	AKI	0.87 (0.77–0.98)	0.70	0.96	Cutoff 1.27 mg/L
	RRT	0.94 (0.88–1.00)	1.00	0.83	Cutoff 3.22 mg/L

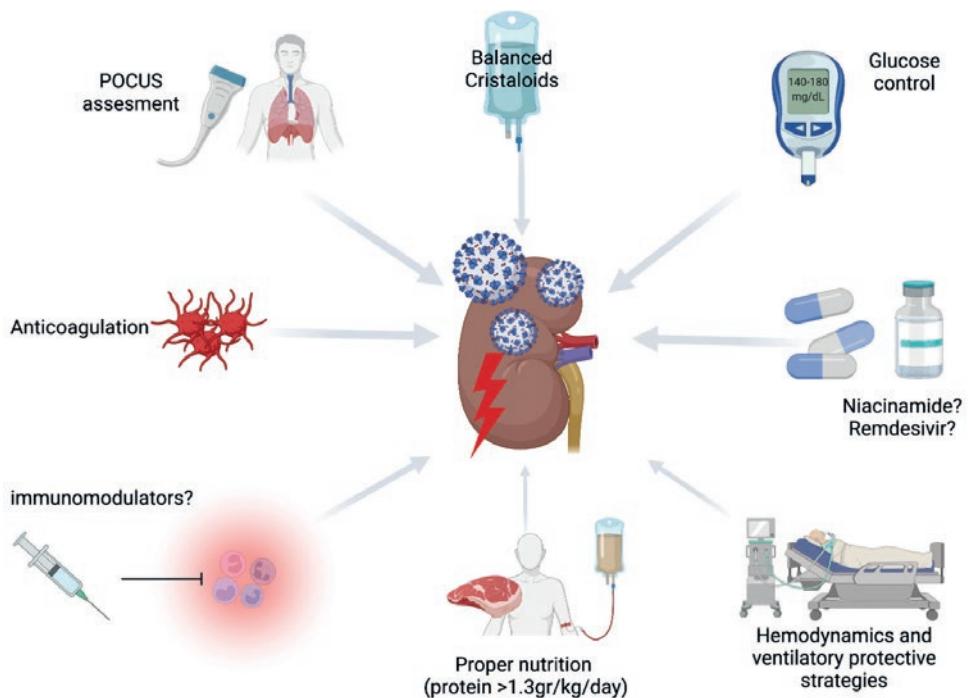
(Continues)

Table 2. Urinary biomarkers in hospitalized patients with C19-AKI^{62, 65-71} (continued)

Biomarkers	Author	AUC (95% CI)	Sensitivity	Specificity	Observations
Functional Biomarker					
Cystatin C	Yildirim et al. ⁷¹	AKI 0.96 (0.90–1.0)	0.90	0.88	n = 348
Tubular Repair-Biomarker					
EGF	Menez et al. ⁶⁹	Composite: AKI-3, RRT, death within 60 days	NR	NR	NR HR = 0.61 (95% CI: 1.09–1.84)

AUC: area under curve; uNGal: urinary neutrophil gelatinase-associated lipocalin; AKI: acute kidney injury; RRT: renal replacement therapy; NR: not registered; uKIM: urinary kidney injury molecule-1; HR: hazards ratio; TIMP-2: tissue inhibitor of metalloproteinase type 2; IGFBP7: Insulin-like growth factor binding protein; EGF: epidermal growth factor.

Figure 2. Management of C19-AKI. Comprehensive management of the patient with C19-AKI includes optimal fluid management, hemodynamic monitoring, glucose control, anticoagulation, nutrition, and immunomodulatory agents, as discussed in the text.



point-of-care ultrasonography (POCUS) could be very useful⁷². In the presence of shock, early initiation of vasopressors is necessary in AKI, and it seems reasonable to apply this approach within the context of COVID-19⁷².

In patients taking RAASi, these should not be discontinued unless strictly necessary²⁶. Interestingly, based

on the pathophysiological mechanism of the entry of SARS-CoV-2 into cells, in a multicenter clinical trial with early COVID-19 patients who were randomized to receive telmisartan 40 mg or placebo every 12 h for 2 weeks, C-reactive protein decreased in cases who received telmisartan; they also had a shorter hospital stay, as well as decreased mortality⁷³. This information is in line with results from other AKI cohorts,

in which the administration of RAASi during or as early as possible after hospitalization improves clinical outcomes.

Other general measures recommended in AKI due to any cause and that are recommended in C19-AKI include avoidance of drugs with nephrotoxic potential (analgesics or aminoglycosides), if possible, avoiding hyperglycemia, and the use of immunomodulatory agents. In hospitalized patients with C19-AKI, hyperglycemia may be secondary to insulin resistance, a hypercatabolic state, and/or the result of dexamethasone (DXM) administration. Glucose levels should be maintained ~140-180 mg/dL and, if necessary, the use of insulin in bolus or infusion is recommended^{74,75}.

Immunomodulatory agents that may potentially attenuate cytokine production such as tocilizumab, sarilumab, anakinra, imatinib, dasatinib, cyclosporin, immunoglobulins, or baricitinib have no demonstrated benefit or effect on the prevention or amelioration of C19-AKI³. Baricitinib is one of the most often used drugs: we must recall that its half-life may extend up to 19 h (normally, 6 h) in patients with severe AKI, and it is rapidly dialyzable³. Remdesivir, an inhibitor of viral RNA polymerase, can improve C19-AKI by modulating macrophage inflammasome activation and the inflammatory immune response⁷⁶. In mice, the drug protects against AKI by specifically inhibiting the NLRP3 inflammasome activation in macrophages, thereby reducing inflammation, and improving the recovery of renal function and the kidney pathological score; however, these effects have not been proven in humans⁷⁶. Further, there is evidence that remdesivir may be associated with the development of AKI, increasing the risk of kidney injury 20-fold. To date, renal function in patients on remdesivir should be closely monitored, and its use should be avoided if the eGFR is < 30 mL/min⁷⁶.

In the RECOVERY trial⁷⁷, DXM treatment improved survival at 28 days in the subgroup of patients with severe (patients with oxygen requirements) and critical (ICU patients) COVID-19⁴⁸. Interestingly, in this study, a lower percentage of patients warranted RRT (4.4% vs. 7.5%, OR = 0.61) if they had received DXM, although renal outcomes were not one of the study's main objectives⁷⁷. Subsequently, in a cohort study of 100 patients with severe COVID-19 conducted by another group, they reported that the systematic use

of DXM prevented the development of AKI (75% vs. 35%, OR = 0.31; CI: 0.09–0.99)⁷⁷.

Anticoagulation has become essential in the treatment of hospitalized patients with COVID-19. AKI is considered to carry a high risk of thrombosis, and prophylactic anticoagulation should be administered. Some anticoagulants should be adjusted to renal function such as low molecular weight heparins (enoxaparin) whose dose should be decreased by half, but not that of unfractionated heparin. In the absence of thrombosis, anticoagulation should be continued for 4 weeks with direct anticoagulants (apixaban and rivaroxaban, which do not require renal dose adjustment), and for 6 months if thrombosis is confirmed during hospitalization⁷⁸.

The nutrition of patients with C19-AKI who do not require RRT should guarantee a protein intake of 1.3–1.5 g/kg/day, and it should be increased if hemodialysis (HD) or continuous kidney replacement therapy (CKRT) are required³.

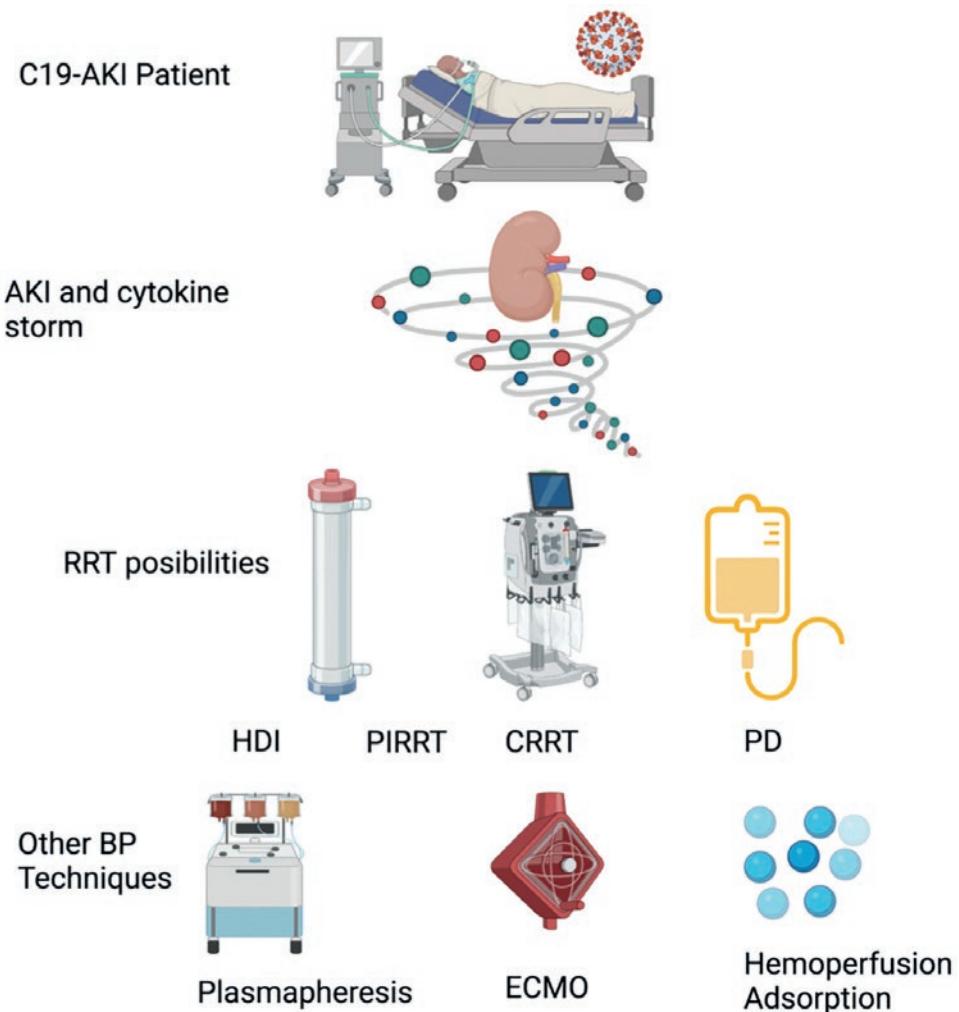
In patients with C19-AKI, kidney injury appears to develop as a result of renal ischemia and acute tubular necrosis with an acquired renal deficiency in intermediate energy metabolism (NAD+: nicotinamide adenine dinucleotide); a deficiency or shortage of this decreases ATP production that, if not controlled, can culminate in tubular dysfunction and cell death⁸⁰. Based on these findings, a cohort study reported that patients who received oral niacinamide (Vitamin B3) had a 36% decrease in their risk of death and the need for RRT, especially in patients with a greater severity score in the KDIGO 2-3 criteria⁸⁰.

In kidney-transplanted patients with C19-AKI, treatment with bamlanivimab or casirivimab-imdevimab and immunosuppression reduction has been tested with some success. Patients treated with monoclonal antibodies developed measurable anti-SARS-CoV-2 IgG with ACE2 receptor blocking activity, and no reported associated deaths or graft losses⁸¹.

RENAL REPLACEMENT THERAPY

In patients with C19-AKI, the indications to initiate RRT remain the same as in patients with AKI unrelated to COVID-19. However, in the early waves of the

Figure 3. Renal replacement therapy (RRT). The options for RRT in C19-AKI are divided into continuous RRT, prolonged intermittent RRT, intermittent hemodialysis, and peritoneal dialysis.



pandemic, when the number of patients was very high, the approach of waiting as long as possible before resorting to RRT was the most common practice⁸².

The options for RRT in C19-AKI patients mainly depend on the center, the availability of the necessary equipment, and the expertise of the medical and nursing staff for the management of different therapies. RRT modalities are divided into continuous RRT (CRRT), prolonged intermittent RRT (PIRRT), intermittent hemodialysis (IHD), and peritoneal dialysis (PD)⁸³ (Fig. 3).

Some cohort studies have recommended CRRT as the first-choice therapy since it leads to better

hemodynamic control in patients that in most cases, were hemodynamically unstable, on IMV, requiring multiple vasopressors, and with an overexpressed inflammatory response. However, many centers did not have CRRT available, or not a sufficient amount to care for all patients in need. Therefore, PIRRT was used instead, and it became a good option, with favorable results⁸³. On the other hand, hemodynamically stable patients or those with emergency indications, such as hyperkalemia or severe metabolic acidosis, were considered for IHD treatment. During this pandemic, PD became a cornerstone of therapy, and proved to be a good option in hemodynamically unstable patients, particularly in those with small-volume refills (1.5 L), as proposed by Ponce et al.⁸⁴. A

Table 3. Blood purification techniques in COVID-19 patients

Technique	Mechanism and examples
HVHF and HCO	HVHF: Convection enhances removal of large molecular proinflammatory cytokines HCO: Large-pore membrane (average 20 nm) allows removal of large cytokine molecules
Hemadsorption and Hemoperfusion (HP)	Membranes coated with heparin or antibiotics. Adsorption of endotoxins and cytokines (Oxiris, Septex) HP involves passage of blood through a hemofilter where mediators are adsorbed to the membrane surface or through a sorbent-containing cartridge (Cytosorb, Toraymyxin, HA330, CPFA): Adsorption of endotoxins and cytokines. (Seraph): Bacteria, viruses, fungi, and toxins
TPE	An extracorporeal technique performed in an apheresis machine in which patient plasma is separated from blood and removed; then, the cellular blood components are returned to the patient together with a replacement fluid

HVHF: high-volume hemofiltration; HCO: high cut-off membrane; HP: hemoperfusion; TPE: therapeutic Plasma Exchange; ECCO₂R: extracorporeal carbon dioxide removal; ECMO: extracorporeal membrane oxygenation.

controversial issue that arose with PD was its use in patients requiring a prone position. However, with these small intra-peritoneal volumes, the patient position did not appear to be a problem, although, according to the world literature, this modality of treatment had been reserved for patients in the supine position⁸⁴.

EXTRACORPOREAL BLOOD PURIFICATION

Patients with severe COVID-19 develop AKI as part of the broad spectrum of MODS, so it was not uncommon for them to require multi-organ support, better known as extracorporeal organ support (ECOS)⁸⁵. ECOS has become a reality and a useful weapon against COVID-19 and its complications. In an attempt to remove inflammatory mediators such as Pathogen-Associated Molecular Patterns (PAMPS), Damage-Associated Molecular Patterns (DAMPS), cytokines, and endotoxins, the use of sequential extracorporeal therapies has become more frequent than ever⁸⁵. Table 3 shows some of the most-used extracorporeal therapies and their rationale. Although these treatment modalities have not reaped major survival benefits, and there is no clear evidence of their benefits in randomized clinical trials, their underlying physiological bases are promising in patients with sepsis and COVID-19⁸⁵.

LONG-TERM OUTCOMES IN C19-AKI

According to observational studies, 30-80% of patients with C19-AKI reach different grades of kidney function recovery at follow-up^{11,13,86}, although little is known about long-term kidney function at 1 year and beyond. In the multicenter cohort study, STOP COVID, of 637 patients admitted to the ICU with AKI and RRT, 63% had died at the end of a median follow-up of 17 days. Of the 216 patients discharged, 34% were still dialysis-dependent at discharge, and 18% at 60 days after ICU admission¹². Another cohort that exclusively included critically ill patients with C19-AKI showed a 74% recovery of kidney function at discharge in cases with AKI without the need for RRT, and 67% in those with AKI and RRT¹³. An even better renal prognosis was found in a retrospective study of patients admitted to the ICU in an U.K. tertiary center, where 82% of patients had full renal recovery at discharge, and 91% recovered at 90 days, defining recovery as sCr < 1.5 times of baseline and no need for RRT⁸⁸. This broad range of outcomes can be explained in part by the heterogeneity of the studied population, different follow-up periods, and the lack of a standardized definition of kidney recovery.

Notably, a cohort study from the United States revealed an accelerated decline in kidney function in patients with C19-AKI and non-RRT during hospitalization, and who survived after discharge. After a

median follow-up of 93 days, their eGFR had decreased more than that of controls with AKI and no COVID-19, with a difference in slope of $-11.3 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$ (95% CI; -22.1 – -0.4 ; $p = 0.04$) in the unadjusted mixed-effects model; $-12.4 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$ (95% CI, -23.7 – -1.2 ; $p = 0.03$) after adjusting for comorbidities; and $-14 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$ (95% CI, -25.1 – -2.9 ; $p = 0.01$) in the adjusted model for comorbidities, peak Scr, and the need for dialysis⁸⁶. This study underscores the relation between C19-AKI and subsequent CKD, as well as its association with a steeper decline in kidney function than in AKI due to other causes; these observations suggest worsening outcomes at follow-up and should alert us as clinicians to manage closely and strictly control CKD progression factors.

To date, the largest registry that has evaluated renal function outcomes after COVID-19 infection was conducted by Bowe et al.⁸⁷. They studied 89,216 patients with COVID-19 and compared them to 1,637,467 controls. At 6 months, COVID-19 survivors had a greater risk of AKI (HR = 1.94 [CI 95%: 1.86–2.04]), their eGFR decreased $\geq 50\%$ (HR = 1.62 [CI 95%: 1.51–1.74]), and their risk for end-stage kidney disease (ESKD) increased (HR = 2.96 [CI 95%: 2.49–3.51]), as did their risk of developing a major adverse kidney event (MAKE) (HR = 1.66 [CI 95%: 1.58–1.74]). The risk increased according to the severity of the disease, whereby non-hospitalized individuals (81.5% of the cohort) had the lowest risk, while hospitalized patients (14%) and those managed in an ICU (4.7%) showed the greatest risk of developing adverse kidney outcomes. When the authors classified patients according to AKI development, hospitalized patients with AKI had a greater risk of ESKD (HR = 4.91 [CI 95%: 3.10–7.77]) and MAKE (HR = 7.37 [CI 95%: 6.03–9.02]), in comparison with non-hospitalized COVID-19 patients. The same phenomenon was observed in terms of ESKD (HR = 3.37 [CI 95%: 1.88–6.06]) and MAKE risks (HR = 2.92 [CI 95%: 2.33–3.65]), in contrast with hospitalized COVID-19 individuals who did not develop AKI. Linear mixed models to characterize post-acute COVID-19 eGFR trajectories showed a greater decline in eGFR in patients with COVID-19 admitted to the ICU: -7.69 (-8.27 – -7.12), -5.2 (-5.24 – -4.16) in hospitalized cases, and -3.26 (-3.58 – -2.94) in outpatients, compared with an average slope of $-0.49 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$ in controls. Likewise,

when patients were stratified by AKI development, a decline in eGFR – 8.41 (CI 95%: -9.72 – -7.10) $\text{mL/min}/1.73 \text{ m}^2/\text{year}$ was observed in hospitalized individuals with AKI, in comparison with a drop of -5.27 (CI 95%: -5.86 – -4.68), and -3.30 (CI 95%: -3.62 – -2.99) in cases that were hospitalized without AKI, and in non-hospitalized patients, respectively⁸⁷. These authors demonstrated the relevance of COVID-19 infection in kidney outcomes during follow-up and adequately revealed how individuals with more severe disease develop more renal function sequelae. The value of this study hinges not only on its sample size but it is also the first study demonstrating that even patients without AKI during the course of COVID-19, have worse renal prognoses in terms of AKI, ESKD, eGFR decline, and MAKE.

In our experience at the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*, in a registry of 60 patients with C19-AKI who required RRT, 29 patients were discharged alive (48%). At 90 days, no patients remained dialysis-dependent, 77% ($n = 23$) reached complete remission, and 20% ($n = 6$) had partial recovery of renal function. Twenty-six (90%) patients have completed their one-year follow-up evaluation. Four individuals (15%) have died and 3 (12%) as a result of urgent dialysis initiation criteria. Furthermore, 12% ($n = 3$) were diagnosed with advanced CKD stages 4–5⁸⁸. These findings are in line with the previous reports throughout the world.

CONCLUSIONS

Despite early reports on the contrary, AKI as a complication of COVID-19 infection is very common in hospitalized patients, and more so in ICU patients requiring IMV. The development of C19-AKI increases the risk of mortality, CKD, and ESRD. The treatment should follow practice guidelines for the general management of AKI given the heterogeneous nature of potential AKI causes. No specific therapies have demonstrated a clear benefit in patients with C19-AKI. In some studies, DXM decreased the need for RRT and the incidence of AKI. Extracorporeal blood therapies appear promising, but at this point it should be preferably tested within the context of a clinical trial. Long-term outcomes of C19-AKI are poor, and these patients should be closely followed considering their poor renal function prognosis.

REFERENCES

1. World Health Organization. Coronavirus Disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update. Geneva: World Health Organization. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
2. Ahmadian E, Khatibi SM, Soofiyani SR, Abediazar S, Shoja MM, Ardalani M, et al. COVID-19 and kidney injury: pathophysiology and molecular mechanisms. *Rev Med Virol*. 2021;31:e2176.
3. Nadim MK, Forni LG, Mehta RL, Connor MJ Jr., Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th acute disease quality initiative (ADQI) workgroup. *Nat Rev Nephrol*. 2020;16:747-64.
4. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney Disease: improving global outcomes. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1-138.
5. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98:209-18.
6. Silver SA, Beaubien-Soulimy W, Shah PS, Harel S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis. *Kidney Med*. 2021;3:83-98.e1.
7. Birkelo BC, Parr SK, Perkins AM, Greevy RA Jr., Hung AM, Shah SC, et al. Comparison of COVID-19 versus influenza on the incidence, features, and recovery from acute kidney injury in hospitalized United States veterans. *Kidney Int*. 2021;100:894-905.
8. Martínez-Rueda AJ, Álvarez RD, Méndez-Pérez RA, Fernández-Camargo DA, Gaytan-Arocha JE, Berman-Parks N, et al. Community- and hospital-acquired acute kidney injury in COVID-19: different phenotypes and dismal prognosis. *Blood Purif*. 2021;50:931-41.
9. Estenssoro E, Loudet CI, Ríos FG, Edul VS, Plotnikow G, Andrian M, et al. Clinical characteristics, and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): a prospective, multicentre cohort study. *Lancet Respir Med*. 2021;9:989-98.
10. Doher MP, De Carvalho FR, Scherer PF, Matsui TN, Ammirati AL, Da Silva B, et al. Acute kidney injury and renal replacement therapy in critically ill COVID-19 patients: risk factors and outcomes: a single-center experience in Brazil. *Blood Purif*. 2021;50:520-30.
11. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. *J Am Soc Nephrol*. 2021;32:161-76.
12. Lumertgul N, Pirondini L, Cooney E, Kok W, Gregson J, Camporota L, et al. Acute kidney injury prevalence, progression and long-term outcomes in critically ill patients with COVID-19: a cohort study. *Ann Intensive Care*. 2021;11:123.
13. Ng JH, Hirsch JS, Hazzan A, Wanchoo R, Shah HH, Malieckal DA, et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. *Am J Kidney Dis*. 2021;77:204-15.e1.
14. Raina R, Mahajan ZA, Vasishta P, Chakraborty R, Mukunda K, Tibrewal A, et al. Incidence and outcomes of acute kidney injury in COVID-19: a systematic review. *Blood Purif*. 2022;51:199-212.
15. Cai X, Wu G, Zhang J, Yang L. Risk factors for acute kidney injury in adult patients with COVID-19: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2021;8:719472.
16. Akilesh S, Nast CC, Yamashita M, Henriksen K, Charu V, Troxell ML, et al. Multicenter clinicopathologic correlation of kidney biopsies performed in COVID-19 patients presenting with acute kidney injury or proteinuria. *Am J Kidney Dis*. 2021;77:82-93.e1.
17. Caza TN, Cassol CA, Messias N, Hannoudi A, Haun RS, Walker PD, et al. Glomerular disease in temporal association with SARS-CoV-2 vaccination: a series of 29 cases. *Kidney 360*. 2021;2:1770-80.
18. Del Toro-Cisneros N, Mejia JM, Caballero-Islas AE, Martinez-Rueda AJ, Hernandez-Flores J, Proaño-Zamudio J, et al. Dexa-methasone reduces AKI in critical COVID-19 patients. *J Am Soc Nephrol*. 2021;32:67.
19. Charytan DM, Parnia S, Khatri M, Petrilli CM, Jones S, Benstein J, et al. Decreasing incidence of acute kidney injury in patients with COVID-19 critical illness in New York City. *Kidney Int Rep*. 2021;6:916-27.
20. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399:1303-12.
21. Michaels MG, La Hoiz RM, Danziger-Isakov L, Blumberg EA, Kumar D, Green M, et al. Coronavirus disease 2019: implications of emerging infections for transplantation. *Am J Transplant*. 2020;20:1768-72.
22. Kremer D, Pieters TT, Verhaar MC, Berger SP, Bakker SJ, Van Zuilen AD, et al. A systematic review and meta-analysis of COVID-19 in kidney transplant recipients: lessons to be learned. *Am J Transplant*. 2021;21:3936-45.
23. Chu C, Zeng S, Hasan AA, Hocher CF, Krämer BK, Hocher B. Comparison of infection risks and clinical outcomes in patients with and without SARS-CoV-2 lung infection under renin-angiotensin-aldosterone system blockade: systematic review and meta-analysis. *Br J Clin Pharmacol*. 2021;87:2475-92.
24. Baral R, White M, Vassiliou VS. Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. *Curr Atheroscler Rep*. 2020;22:61.
25. Lee SA, Park R, Yang JH, Min IK, Park JT, Han SH, et al. Increased risk of acute kidney injury in coronavirus disease patients with renin-angiotensin-aldosterone-system blockade use: a systematic review and meta-analysis. *Sci Rep*. 2021;11:13588.
26. Lopes RD, Macedo AV, Silva PG, Moll-Bernardes RJ, Santos TM, Mazza L, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with covid-19: a randomized clinical trial. *JAMA*. 2021;325:254-64.
27. Kellum JA, Van Till JW, Mulligan G. Targeting acute kidney injury in COVID-19. *Nephrol Dial Transplant*. 2020;35:1652-62.
28. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the pre-fusion conformation. *Science*. 2020;367:1260-3.
29. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol*. 2020;318:H1084-90.
30. Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? *Am J Physiol Renal Physiol*. 2020;318:F1454-62.
31. Yamaguchi T, Hoshizaki M, Minato T, Nirasawa S, Asaka MN, Niiyama M, et al. ACE2-like carboxypeptidase B38-CAP protects from SARS-CoV-2-induced lung injury. *Nat Commun*. 2021;12:6791.
32. Kuba K, Yamaguchi T, Penninger JM. Angiotensin-converting enzyme 2 (ACE2) in the pathogenesis of ARDS in COVID-19. *Front Immunol*. 2021;12:73269.
33. Bergthaler A, Puchhammer-Stoeckl E, Mirazimi A, Montserrat N, Zhang H, Slutsky AS, et al. Human recombinant soluble ACE2 in severe COVID-19. *Lancet Respir Med*. 2020;8:1154-8.
34. Armaly Z, Kinaneh S, Skorecki K. Renal manifestations of COVID-19: physiology and pathophysiology. *J Clin Med*. 2021;10:1216.
35. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med*. 2020;383:590-2.
36. Sridhar S, Nicholls J. Pathophysiology of infection with SARS-CoV-2-what is known and what remains a mystery. *Respirology*. 2021;26:652-65.
37. Caramaschi S, Kapp ME, Miller SE, Eisenberg R, Johnson J, Eperly G, et al. Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. *Mod Pathol*. 2021;34:1614-33.
38. Han X, Ye Q. Kidney involvement in COVID-19 and its treatments. *J Med Virol*. 2021;93:1387-95.
39. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98:219-27.
40. Peleg Y, Kudose S, D'Agati V, Siddall E, Ahmad S, Nickolas T, et al. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int Rep*. 2020;5:940-5.
41. Wu H, Larsen CP, Hernandez-Arroyo CF, Mohamed MM, Caza T, Sharshir M, et al. AKI and collapsing glomerulopathy associated with COVID-19 and APOL1 high-risk genotype. *J Am Soc Nephrol*. 2020;31:1688-95.
42. Shetty AA, Tawhari I, Safar-Boueri L, Seif N, Alahmadi A, Gariglio R, et al. COVID-19-associated glomerular disease. *J Am Soc Nephrol*. 2021;32:33-40.

43. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, et al. Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol*. 2020;31:1959-68.

44. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of immune response during SARS-CoV-2 infection: lessons from the past. *Front Immunol*. 2020;11:1949.

45. Afzali B, Noris M, Lambrecht BN, Kemper C. The state of complement in COVID-19. *Nat Rev Immunol*. 2022;22:77-84.

46. Pfister F, Vonbrunn E, Ries T, Jäck HM, Überla K, Lochnitz G, et al. Complement activation in kidneys of patients With COVID-19. *Front Immunol*. 2021;11:594849.

47. Yu J, Gerber GF, Chen H, Yuan X, Chaturvedi S, Braunstein EM, et al. Complement dysregulation is associated with severe COVID-19 illness. *Haematologica*. 2022;107:1095-105.

48. Satyam A, Tsokos MG, Brook OR, Hecht JL, Moulton VR, Tsokos GC. Activation of classical and alternative complement pathways in the pathogenesis of lung injury in COVID-19. *Clin Immunol*. 2021;226:108716.

49. Annane D, Heming N, Grimaldi-Bensouda L, Frémeaux-Bacchi V, Vigan M, Roux AL, et al. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: a proof-of-concept study. *EClinical Medicine*. 2020;28:100590.

50. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct Target Ther*. 2021;6:255.

51. Zanza C, Romenskaya T, Manetti AC, Franceschi F, La Russa R, Bertozi G, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. *Medicina (Kaunas)*. 2022;58:144.

52. Martonik D, Parfieniuk-Kowarda A, Rogalska M, Flisiak R. The role of Th17 response in COVID-19. *Cells*. 2021;10:1550.

53. Cortegiani A, Ippolito M, Greco M, Granone V, Prott A, Gregoretti C, et al. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology*. 2021;27:52-66.

54. Hellman T, Usualo P, Järvisalo MJ. Renal replacement techniques in septic shock. *Int J Mol Sci*. 2021;22:10238.

55. Gérard AO, Laurain A, Fresse A, Parassol N, Muzzone M, Rocher F, et al. Remdesivir and acute renal failure: a potential safety signal from disproportionality analysis of the WHO safety database. *Clin Pharmacol Ther*. 2021;109:1021-4.

56. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired Type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020;369:718-24.

57. Perico L, Benigni A, Casiraghi F, Ng LF, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol*. 2021;17:46-64.

58. Shahri MK, Niazkar HR, Rad F. COVID-19 and hematology findings based on the current evidences: a puzzle with many missing pieces. *Int J Lab Hematol*. 2021;43:160-8.

59. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol*. 2021;113:45-57.

60. Husain-Syed F, Ferrari F, Sharma A, Danesi TH, Bezerra P, Lopez-Giacoman S, et al. Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery. *Nephrol Dial Transplant*. 2019;34:308-17.

61. Chávez-Íñiguez JS, Cano-Cervantes JH, Maggiani-Aguilera P, Lavelle-Góngora N, Marcial-Meza J, Camacho-Murillo EP, et al. Mortality and evolution between community and hospital-acquired COVID-AKI. *PLoS One*. 2021;16:e0257619.

62. Casas-Aparicio G, La Barrera CA, Escamilla-Illescas D, León-Rodríguez I, Del Río-Estrada PM, Calderón-Dávila N, et al. Role of urinary kidney stress biomarkers for early recognition of subclinical acute kidney injury in critically ill COVID-19 patients. *Biomolecules*. 2022;12:275.

63. Morita Y, Kurano M, Jubishi D, Ikeda M, Okamoto K, Tanaka M, et al. Urine sediment findings were milder in patients with COVID-19-associated renal injuries than in those with non-COVID-19-associated renal injuries. *Int J Infect Dis*. 2022;117:302-11.

64. Kashani, K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25.

65. Xu K, Shang N, Levitan A, Corker A, Kudose S, Yaeh A, et al. Elevated neutrophil gelatinase-associated lipocalin is associated with the severity of kidney injury and poor prognosis of patients with COVID-19. *Kidney Int Rep*. 2021;6:2979-92.

66. Shakked NP, De Oliveira MH, Cheruiyot I, Benoit JL, Plebani M, Lippi G, et al. Early prediction of COVID-19-associated acute kidney injury: are serum NGAL and serum cystatin C levels better than serum creatinine? *Clin Biochem*. 2022;102:1-8.

67. He L, Zhang Q, Li Z, Shen L, Zhang J, Wang P, et al. Incorporation of urinary neutrophil gelatinase-associated lipocalin and computed tomography quantification to predict acute kidney injury and in-hospital death in COVID-19 patients. *Kidney Dis (Basel)*. 2021;7:120-30.

68. Vogel MJ, Mustroph J, Staudner ST, Leininger SB, Hubauer U, Wallner S, et al. Kidney injury molecule-1: potential biomarker of acute kidney injury and disease severity in patients with COVID-19. *J Nephrol*. 2021;34:1007-18.

69. Menez S, Medina DG, Thiessen-Philbrook H, Wilson FP, Obeid W, Simonov M, et al. Prognostic significance of urinary biomarkers in patients hospitalized with COVID-19. *Am J Kidney Dis*. 2022;79:257-67.e1.

70. Pangan B, Pornillos MC, Guevara D, Poblete J, Besa JJ, Masa-mayor EM, et al. POS-075 accuracy of urine biomarkers tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein-7 ([TIMP-2]:[IGFBP-7]) in predicting acute kidney injury among adult hospitalized Covid-19 patients. *Kidney Int Rep*. 2022;7:S31-2.

71. Yildirim C, Ozger HS, Yasar E, Tombul N, Gulbahar O, Yildiz M, et al. Early predictors of acute kidney injury in COVID-19 patients. *Nephrology (Carlton)*. 2021;26:513-21.

72. Koratala A, Ronco C, Kazory A. Need for objective assessment of volume status in critically ill patients with COVID-19: the Tri-POCUS approach. *Cardiorenal Med*. 2020;10:209-16.

73. Duarte M, Pelorosso F, Nicolosi LN, Salgado MV, Vetulli H, Aquieri A, et al. Telmisartan for treatment of Covid-19 patients: an open multicenter randomized clinical trial. *EClinicalMedicine*. 2021;37:100962.

74. Bellido V, Pérez A. Inpatient hyperglycemia management and COVID-19. *Diabetes Ther*. 2021;12:121-32.

75. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet*. 2019;394:1949-64.

76. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693-704.

77. Orioux A, Khan P, Prevel R, Gruson D, Rubin S, Boyer A. Impact of dexamethasone use to prevent from severe COVID-19-induced acute kidney injury. *Crit Care*. 2021;25:249.

78. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. *Blood Rev*. 2021;47:100761.

79. Tran MT, Zsengeller ZK, Berg AH, Khankin EV, Bhasin MK, Kim W, et al. PGC1 α drives NAD biosynthesis linking oxidative metabolism to renal protection. *Nature*. 2016;531:528-32.

80. Raines NH, Ganatra S, Nissaisorakarn P, Pandit A, Morales A, Asnani A, et al. Niacinamide may be associated with improved outcomes in COVID-19-related acute kidney injury: an observational study. *Kidney 360*. 2020;2:33-41.

81. Aleem A, Slenker AK. Monoclonal Antibody Therapy for High-risk Coronavirus (COVID 19) Patients with Mild to Moderate Disease Presentations. In: StatPearls Treasure Island (FL): StatPearls Publishing; 2022.

82. Granado RC, Casas-Aparicio G, Rosa-Diez G, Rizo-Topete L, Ponce D. Renal replacement therapy for acute kidney injury in COVID-19 patients in Latin America. *Kidney Blood Press Res*. 2020;45:775-83.

83. Ramirez-Sandoval JC, Gaytan-Arocha JE, Xolalpa-Chávez P, Mejia-Vilete JM, Arvizu-Hernandez M, Rivero-Sigarroa E, et al. Prolonged intermittent renal replacement therapy for acute kidney injury in COVID-19 patients with acute respiratory distress syndrome. *Blood Purif*. 2021;50:355-63.

84. Ponce D, Balbi AL, Durand JB, Moretta G, Divino-Filho JC. Acute peritoneal dialysis in the treatment of COVID-19-related acute kidney injury. *Clin Kidney J*. 2020;13:269-73.

85. Ankawi G, Neri M, Zhang J, Breglia A, Ricci Z, Ronco C. Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls. *Crit Care*. 2018;22:262.

86. Nugent J, Akilu A, Yamamoto Y, Simonov M, Li F, Biswas A, et al. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. *JAMA Netw Open*. 2021;4:e211095.

87. Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. *J Am Soc Nephrol*. 2021;32:2851-62.

88. Del Toro-Cisneros N, Martínez-Rojas M, Bobadilla N, Vega-Vega O. POS-848 Serpina3 in predicting renal recovery from acute kidney injury in critically COVID-19 patients. *Kidney Int Rep*. 2022;7:S366.