ACUTE KIDNEY INJURY IN PATIENTS WITH COVID-19: A CHALLENGE FOR NEPHROLOGISTS

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Acute kidney injury (AKI) is a common finding in patients with coronavirus disease 2019 (COVID-CoV-19), and it is associated with long-term hospital treatment, more frequent admission to intensive care units (ICUs), and higher mortality compared with COVID-CoV-19 patients without kidney disease. Moreover, mortality rate is directly proportional to the severity of AKI. The pathophysiology of COVID-19 associated AKI could be related to specific and unspecific mechanisms. COVID-19 - specific mechanisms are direct cellular injury resulting from viral entry through the ACE-2 receptor, which is highly expressed in the kidney, an imbalanced renin-angiotensin-aldosterone system (RAAS), severe respiratory failure, proinflammatory cytokines elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, coagulopathy, microangiopathy, and collapsing glomerulopathy. Nonspecific mechanisms include hemodynamic alterations, high levels of positive end-expiratory pressure in patients requiring mechanical ventilation, sepsis, hypovolemia, rhabdomyolysis, and administration of nephrotoxic drugs. Today, we do not know enough about the prevention and management of COVID-19. Treatment of AKI includes general management, pharmacological management of COVID-19, hemodynamic and volume optimization, renal replacement therapy, and other extracorporeal organ support. As of now, long-term prognosis is unknown. However, it may be safe to speculate that prognosis will be associated to the etiology of AKI. Patients with thromboembolic complications and collapsing glomerulopathy may develop a more severe degree of chronic kidney disease compared to those with other types of renal injury (e.g., acute tubule-interstitial nephritis). Early studies suggest that about one-third of patients who survived AKI caused by COVID-19 will remain dialysis-dependent.

Key words: acute respiratory distress syndrome, acute kidney injury, angiotensin-converting enzyme 2 receptor, COVID-19, cytokine release syndrome, extracorporeal organ support, renal replacement therapy, SARS-CoV-2

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On April 9, 2021, 133,552,774 confirmed cases of coronavirus disease 2019 (COVID-19) including 2,894,295 confirmed deaths were reported by the World Health Organization (WHO) (1). Since the onset of the new severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) outbreak, a lot of research has been focused on pulmonary complications, namely, acute respiratory distress syndrome (ARDS), which is the leading condition in intensive care unit (ICU) admission and associated with a high mortality rate (2-5). Initially, little attention was paid to kidney abnormalities, primarily acute kidney injury (AKI) (7). However, today, it is evident that AKI is prevalent in patients with COVID-19 and that SARS-CoV-2 specifically invades the kidneys. Moreover, a recently published study that utilized autopsy specimens from patients who died from COVID-19 demonstrated evidence for the SARS-CoV-2 invasion of the kidney tissue, along with significant tubular epithelial and peritubular capillary endothelial injury, as well as glomerular changes (8, 9).

EPIDEMIOLOGY

Acute kidney injury is strongly associated with increased mortality and morbidity, and is a complication that can occur during progression of COVID-19 in patients suffering from chronic kidney disease (CKD), as well as in those who are not sick (10). According to the analysis of several studies, the incidence of AKI varies from 0.5% to 23%, with higher rates reported in countries outside China (11). The pooled incidence of COVID-19-associated AKI in different regions of China from 26 peer-reviewed studies was 6.5%, with a much higher rate in patients admitted to ICU (32.5%) than in patients treated at non-intensive departments (5.1%) (12). Studies from Wuhan showed a higher AKI incidence (9.7%) (6) than studies from other provinces in China (2.8%) (12), which may be explained by difference in disease severity.

Recently published studies on COVID-19 worldwide report AKI rates in hospitalized patients of 17.9%-

72.7% in Italy, 9.2%-18.3% in Korea, 19.7%-69.2% in Spain, 5.8%-56.9% in the USA, 52.2%-74.6% in Germany, and 4.7%-64.1% in France and Belgium, which are much higher than the rates in China (12-17). The difference may be explained by the fact that only very sick COVID-19 patients were admitted to hospitals in those countries compared to the admission of less sick patients in China. Health care systems and policies for hospitalization and assigning levels of care are widely different across the world, as well as demographic characteristics, risk factors, morbidities, definition of AKI, and admission rate of COVID-19 patients (Table 1).

Patients who developed AKI had a more critical prognosis in terms of mortality rate compared with those that had only chronic illness as comorbidity (e.g., diabetes mellitus, arterial hypertension, cardiovascular diseases, chronic respiratory diseases and neoplasms). AKI increased the risk of death 5.3 times in these patients (18). In patients with COVID-19, mortality rates increase with age, as well as with the number of chronic pre-existing diseases (especially CKD) (19). All these observations suggest that mortality rate from AKI may be 13 times higher, and that either the presence of CKD at hospital admission or development of AKI during the COVID-19 infection have been both recognized as two independent risk factors for mortality (19, 20).

Table 1.
Potential risk factors for COVID-19 acute kidney injury (AKI)

Demographic risk factors	Risk factors for AKI at admission	Risk factors for AKI during hospitalization
Older age	Severity of COVID-19	Nephrotoxins (e.g., drugs, contrast exposure)
Hypertension	Degree of viremia	Vasopressors
Diabetes mellitus	Respiratory status	Fluid dynamics (fluid overload/hypovolemia)
Cardiovascular diseases	Non-respiratory organ involvement	Ventilation, high positive end-expiratory pressure
Chronic kidney disease	Leukocytosis	
High body mass index	Lymphopenia	
Immunosuppressed state	Hypovolemia/ dehydration	
Genetic risk factors (e.g., APOL1 genotype, ACE-2 polymorphisms)	Elevated markers of inflammation (e.g., CRP, D-dimers, ferritin)	
Smoking history	Rhabdomyolysis	
	Medication exposure (e.g., ACEi, ARB, statin, NSAID)	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; NSAID, nonsteroidal anti-inflammatory drug

ETIOLOGY

Coronaviruses are a group of single-stranded RNA viruses with positive polarity, belonging to the Coronavirus family. Until 2019, six coronavirus strains, which were able to infect humans, were known. Four strains usually circulate in the human population causing mild respiratory infections. In 2003 and 2012, the first two zoonotic strains of coronaviruses capable of infecting humans through an animal were identified. These caused severe lung syndromes in recent times, i.e. the severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) viruses in 2012 (21). In December 2019, unusual cases of pneumonia were reported in the city of Wuhan, located in the Hubei Province in central China. On January 12, 2020, the WHO stated that the disease was caused by a novel coronavirus named SARS-CoV-2. The resulting SARS-CoV-2 related disease was defined as a novel COVID-19 that rapidly spread throughout China, followed by an increasing number of cases in all continents, resulting in a global pandemic (19).

It has been documented that SARS-CoV-2 is a chimeric virus resulting from pre-existing viruses, namely, a bat coronavirus and a coronavirus of unknown origin. Its genomic sequence corresponds to the bat coronavirus with 88% identity and the pangolin coronavirus with 99% identity (22, 23). The genetic analysis performed on the pangolin coronavirus involved only a specific site known as the receptor-binding domain (24). However, it emerged that SARS-CoV-2 and the pangolin coronavirus did not share the same structural characteristics. Therefore, pangolin was identified as the intermediate species of transition from bat to humans rather than being directly responsible for the SARS-CoV-2 pandemic (23, 25). Common routes of transmission of this highly contagious virus are as follows: 1) close contact (the most usual way of infection); 2) transmission *via* aerosols; 3) it has been identified in tears and conjunctival secretions of COVID-19 patients; and 4) SARS-CoV-2 has been found in gastrointestinal tissue of COVID-19 patients (26).

PATHOPHYSIOLOGY

The genomic sequence of SARS-CoV-2 was compared with SARS-CoV and MERS-CoV, and it was found that SARS-CoV-2 has a sequence identity of 79% with SARS-CoV and 50% with MERS-CoV. Upon analysis of certain proteins (coronavirus main proteinase, papain-like protease and RNA-dependent RNA polymerase), it was observed that the sequence identity value between SARS-CoV and SARS-CoV-2 is 96%, on the basis of which it was concluded that there is a similarity in the pathophysiological effects of these two coronaviruses (27).

The SARS-CoV-2 infection represents a major challenge to our homeostatic response. The renin-angiotensin-aldosterone system (RAAS) is a key homeostatic system within our bodies that involves the lung, kidneys, brain, liver and other organs, to regulate fluid volume, blood pressure and electrolyte balance. The first step in COVID-19 pathogenesis is viral invasion *via* its target host cell receptors. SARS-CoV-2 is mostly transmissible through large respiratory droplets, directly infecting cells of the upper and lower respiratory tract, especially nasal ciliated and alveolar epithelial cells. In addition to the lungs, angiotensin-converting enzyme 2 (ACE-2) receptors are also expressed in various other human tissues such as the kidneys, small intestine, heart, thyroid, testis, and adipose tissue, indicating that the virus may directly infect cells of other organ systems when viremia is present. ACE-2 is a carboxypeptidase expressed on the cell surface that cleaves angiotensin I (Ang I) into angiotensin 1-9 and angiotensin II (Ang II) into angiotensin 1-7, counteracting the vasoconstrictor, proliferative and fibrotic effects of angiotensin II generated by angiotensin converting enzyme (ACE). It now appears that the ACE-2 receptor, which is ubiquitous throughout our bodies, facilitates entry of SARS-CoV-2 into host cells and disrupts the normal homeostatic response.

However, for many coronaviruses, including SARS-CoV-2, host cell binding alone is insufficient to facilitate viral and cell membrane fuse, requiring S-protein priming or cleavage by host cell proteases or transmembrane serine proteases. Recently, it was demonstrated that S-protein priming by transmembrane serine protease 2 (TMPRSS2) is required to facilitate SARS-CoV-2 entry into host cells (28).

After entering the cell and becoming activated, SARS-CoV-2 uses the endogenous transcription mechanism of the cells to replicate and spread. Cells infected by SARS-CoV-2 can recruit and modulate immune cells through secretion of chemokines or cytokines. The interaction between macrophages and cells expressing ACE-2 suggest a primary role of macrophages as a sentinel during viral infection. A recent study, however, has shown a downregulation of mitochondrial proteins that interact with SARS-CoV-2. This mechanism could be interpreted as a process through which the virus prevents apoptosis induced by mitochondria (29, 30).

Finally, targeting of ACE-2 by SARS-CoV-2 results in angiotensin dysregulation, innate and adaptive immune pathway activation, hyper-coagulation, and consequent multiple organ damage (Figure 1).

Epithelial cells of the lungs and gut are prime target of SARS-CoV-2 infection and COVID-19 symptoms. The expression of ACE-2 has been shown also in the kidney, heart, liver, esophagus, stomach, ileum, colon, and epithelial cells in the nose and mouth (31, 32). These data associated with the evidence that reduction of taste and/or smell, myocardial dysfunction with acute cardiovascular events, gastrointestinal disorders and AKI are among the most frequent clinical manifestations of COVID-19, suggest that SARS-CoV-2 can infect these organs causing functional damage.
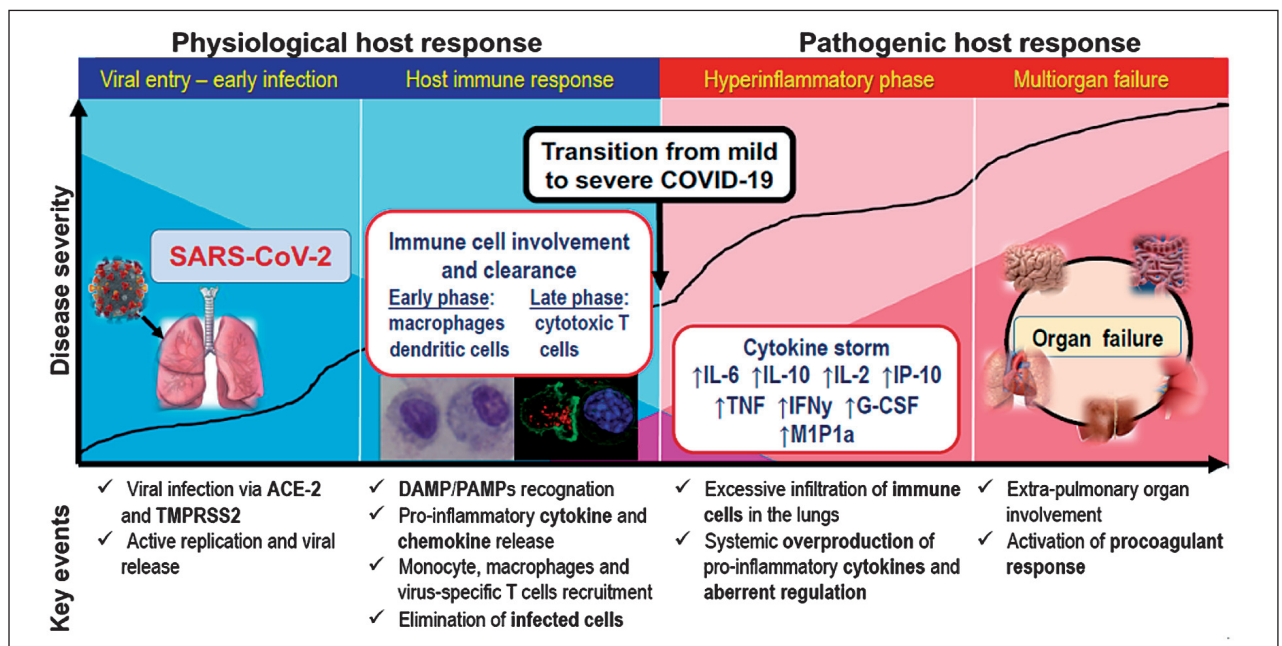

Fig. 1. *Key developments during COVID-19 infection.*
Dark blue shading indicates physiologic viral host response over time; dark red shading indicates pathogenic hyper-inflammatory host response over time.

PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY CAUSED BY SARS-COV-2

Recent studies with SARS-CoV-2 infected patients have reported that human kidney is a specific target for COVID-19 infection (33, 34). The presence of viral particles in the renal tubular epithelium, which were morphologically identical to SARS-CoV-2, and with viral arrays and other features of virus assembly, provide evidence for a productive direct infection of the kidney by SARS-CoV-2. This finding offers confirmatory evidence that direct renal infection occurs in the setting of AKI in COVID-19 (35). Further, Diao *et al.* (36) examined viral nucleocapsid protein in the kidney of postmortem patients and found that SARS-CoV-2 antigens accumulated in renal epithelial tubules, suggesting that SARS-CoV-2 infects the human kidney directly, which leads to kidney dysfunction and contributes to viral spreading in the body. An additional study of 26 autopsies found virus particles characteristic of SARS-CoV-2 in the proximal tubular epithelium and podocytes by electronic microscopy. This finding was associated with foot process effacement and occasional vacuolation and detachment of podocytes from the glomerular basement membrane (9).

However, several articles disputed whether the particles identified were virus in origin and suggested that multivesicular bodies or clathrin-coated vesicles had an identical appearance (37). Although direct viral infection of the kidney is possible, it is certainly not a common or even widespread finding reported.

The results of these, but also numerous other researches, along with the consensual physiological role of ACE-2 in the kidneys, raise the possibility of a complex multifactorial pathophysiology explaining kidney abnormalities in COVID-19, involving a direct cytopathic effect of the virus, local disruption in RAAS homeostasis, and a systemic inflammatory response to infection (Figure 2).
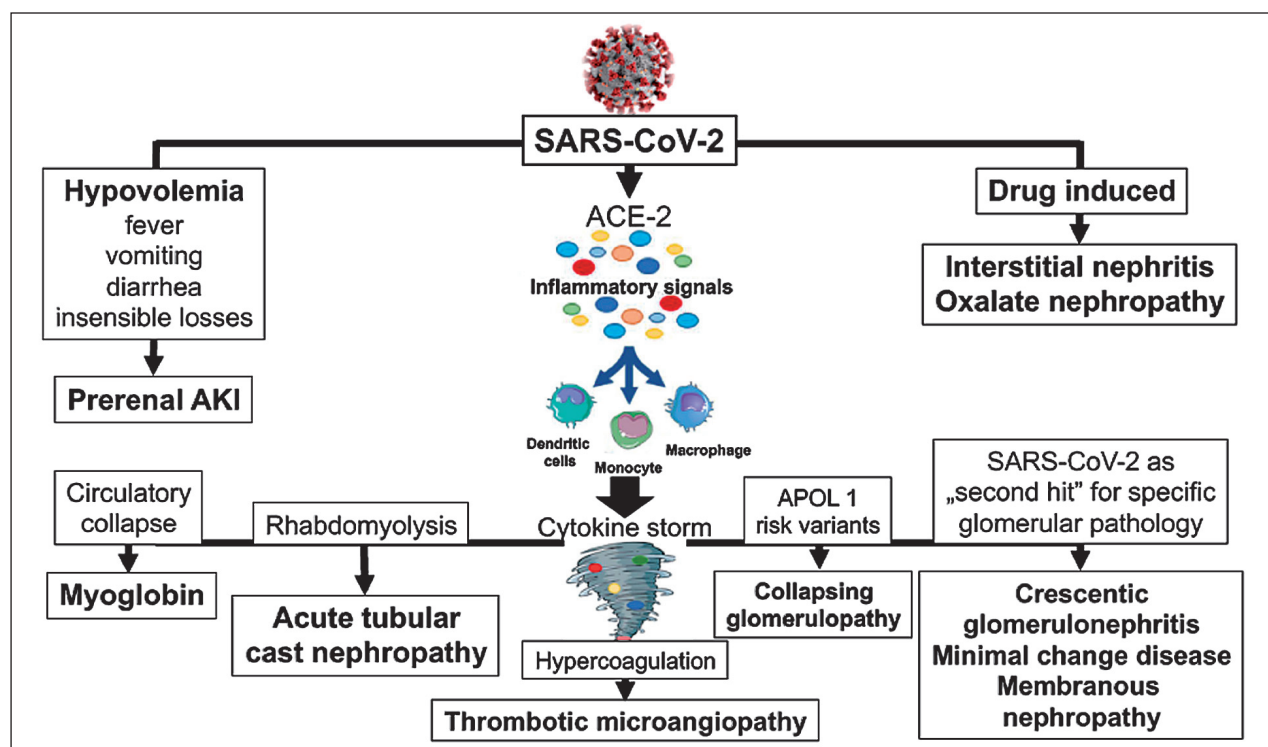

Fig. 2. *Pathophysiology of acute kidney injury caused by SARS-CoV-2.*

Aberrant immune host response together with cytokine storm and lymphocytopenia, followed by ARDS, are relevant problems that influence the severity of COVID-19, and modulation of the immune response and inflammation may thus be considered crucial (37).

ARDS, acute respiratory distress syndrome

Angiotensin II pathway activation

Interaction between SARS-CoV-2 and angiotensin II receptors has been proposed as a potential mechanism contributing to the virus infectivity. The main binding site for SARS-CoV-2 is the ACE-2 protein, which is expressed by the kidney much more than the lungs (37, 38). ACE-2 is expressed on the brush border apical membrane of the proximal tubule, where it colocalizes with ACE. It is also present at lower levels in podocytes. The virus could enter the kidney by invading podocytes first. Injured podocytes often are shed in

urine and podocytes harboring viral particles if shed in urine may contribute to the disease transmission in the proximal tubules (Figure 3). Coronavirus entry into the host target cells also requires fusion of the viral envelope with cellular membranes. Fusion-activated SARS-CoV-2 peptides are created by specific proteolytic cleavage of the S proteins, in a step called 'priming'. As a consequence, cell infectivity not only depends on ACE-2 expression, but is also governed by the types of proteases found in a given cell type. In the kidney, TMPRSS2, which primes the SARS-CoV-2 S protein, is robustly expressed in the distal nephron rather than the proximal tubule. It remains to be determined if other TMPRSS such as TMPRSS 4, 5, or 9in the proximal tubule can mediate the priming step. Therefore, the coexpression of ACE-2 and TMPRSS2 is a determining factor for the entry of SARS-CoV-2 into the host cells (19).

After entering the cell and becoming activated, SARS-CoV-2 uses the endogenous transcription mechanism of the cells to replicate and spread (19). Cells infected by SARS-CoV-2 can recruit and modulate immune cells through the secretion of chemokines or other cytokines. The role of macrophages remains to be defined. In fact, the interaction between macrophages and cells expressing ACE-2 is known, suggesting a primary role of macrophages as a sentinel during viral infection. A recent study has shown downregulation of mitochondrial proteins that interact with SARS-CoV-2. By that mechanism, the virus prevents apoptosis induced by mitochondria (30).

Viral replication in podocytes and the consequent podocyte injury during COVID-19 infection is a great challenge for the patients to deal with and to the nephrologists to strategize treatment options.
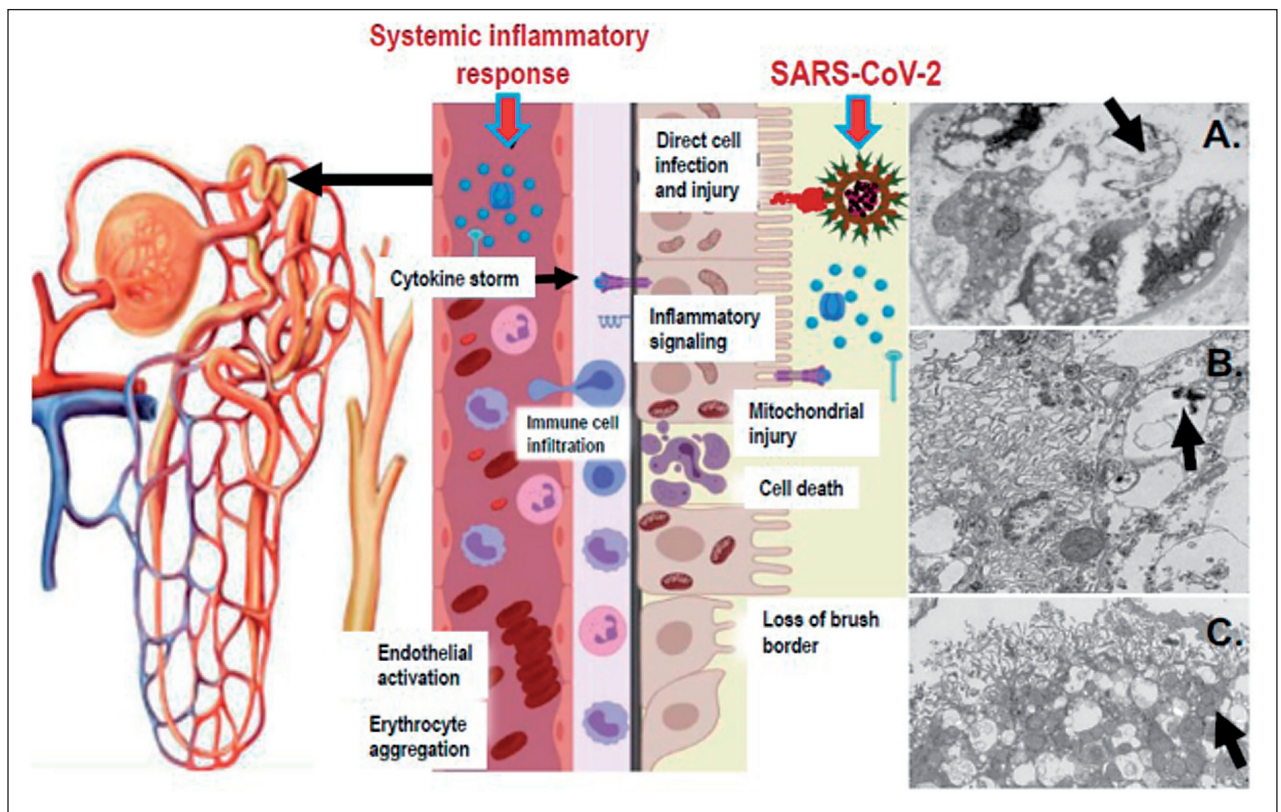

Fig. 3. *Possible mechanisms of kidney damage by severe SARS-CoV-2 infection.*

Angiotensin-converting enzyme 2 expression in proximal epithelial cells makes them a direct target of SARS-CoV-2 infection and virus-related injury. This process could be aggravated first by local inflammation,and after that uncontrolled systemic inflammatory response involving a cytokine storm.
A. Electron micrograph of proximal tubule with severe epithelial cell injury with cell sloughing and denudation of the basement membrane (fragments of membranes appear in the lumen – arrow). The nuclei appear pyknotic and the cytoplasm severely vacuolated.
B. Cytoplasmic dissolution and widespread densities consistent with damaged phospholipids suggestive of oxidative membrane injury (arrow).
C. Disintegration of the brush border and extensive cytoplasmic vesiculation. The mitochondria appear markedly swollen. The clusters of small mitochondria are kept in places (arrow).

Customized according to: Papadimitriou JC et al. Kidney Int Rep. (2020) doi: https://doi.org/10.1016/j.ekir.2020.10.029(8); Martinez-Rojas MA et al. Am J Physiol Renal Physiol. 2020; 318: F1454-62 (33).

Even more, regardless of direct viral infection of the kidney, ACE-2 is increased in the context of acute lung injury and there is evidence that it is downregulated in AKI. This may lead to type 1 angiotensin receptor activation, as well as decreased angiotensin (1-7) formation and subsequent worsening of AKI (Figure 4), which has special significance in the subpopulation of patients with diabetes mellitus (DM), cardiovascular disease (CVD), and CKD (Table 1).Thus, patients with CKD, especially those with diabetic kidney disease (DKD), who develop COVID-19 may be at a higher risk of AKI because of baseline upregulation of the ACE and downregulation of ACE-2, a combination that primes a proinflammatory (including complement activation) and profibrotic state in the kidneys of those with DKD. Pre-existent CKD could worsen the expected outcomes of patients with COVID-19 and may involve many pathophysiological mechanism is dependent on comorbidities (39).
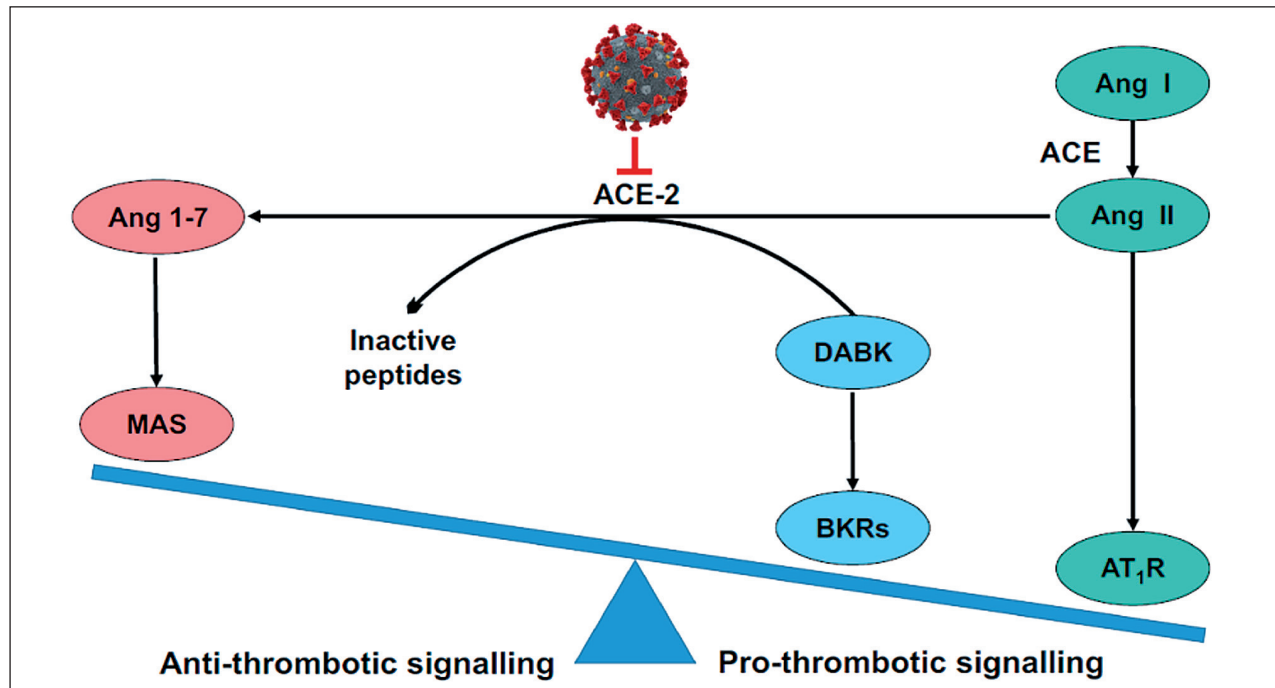

Fig. 4. *Effect of SARS-CoV-2 infection on endothelial cell function.*
SARS-CoV-2 directly infects endothelial cells owing to their high expression levels of ACE-2 and TMPRSS2. After binding by SARS-CoV-2, ACE-2 is internalized, and downregulated on endothelial cells, which favor progression of inflammatory and pro-fibrotic processes in the lung,kidney, heart and some other organs, triggered by Ang II hyperactivity. Inhibition of ACE-2 by binding of SARS-CoV-2 reduces the ACE-2 mediated conversion of Ang II to Ang 1-7, which act on the MAS receptor. The reduction of MAS receptor activation induces a pro-inflammatory phenotype through increased activation of AT1Rs. Furthermore, reduced expression of ACE-2 might in turn indirectly activate the KKS, which ultimately leads to increased vascular permeability (60). Additionally, reduction in the levels of ACE-2 limits degradation of DABK into inactive peptides, ultimately leading to increased pro-thrombotic signaling via the activation of BKRs.
ACE-2, angiotensin-converting enzyme 2; Ang 1-7, angiotensin 1-7; Ang II, angiotensin II; AT1R, type 1 angiotensin receptor; BKR, bradykinin receptors; DABK, des-Arg9 bradykinin; KKS, kallikrein-kinin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine 2

Dysregulation of immune response and cytokine storm

Renal impairment in patients with COVID-19 is partly due to acute tubular necrosis (ATN) resulting from the direct influence of SARS-CoV-2, but also indirectly through the complex immune mechanisms triggered by cellular damage. Histopathologic examination performed on kidney specimens obtained from autopsy of COVID-19 patients with AKI showed viral antigens in the cytoplasm of tubular cells, C5b-9 depositions on the apical brush border of tubular epitheli-al cells, and presence of CD68+ macrophages in the tubul-interstitium (19). Recent research has revealed that patients infected by SARS-CoV-2 showed lymphopenia, mainly related to the significant reduction in absolute T cell counts, particularly cytotoxic T lymphocytes (CD8+), increased neutrophil counts, and elevated levels of proinflammatory interleukins (IL-2, IL-6, IL-10) and interferon-γ (IFN-γ). It is known that T cells are important for dampening overactive innate immune responses, and that a loss of T cells during viral infection may result in enhanced inflammatory responses. Moreover, it has been observed that when

the T cell count drops serum levels of IL-2, IL-4, IL-10, INF, and tumor necrosis factor-α (TNF-α) (40). Due to the decrease in CD4+, CD8+ and NK lymphocytes, COVID-19 patients with more severe clinical manifestations have higher serum concentrations of IL-6 and lower IFN-γ than those with mild forms of the disease.

Normally, the IFN-receptor binding induces a cascade of signals with activation of the genes coding for proteins with antiviral, anti-proliferative or immunomodulatory properties (41), but in patients infected by SARS-CoV-2, a higher IL-6/IFN-γ ratio can be related to an enhanced cytokine storm (42). These observations suggest that in patients with COVID-19, AKI may have an inflammatory etiology mediated by a cytokine storm, an inflammatory process that originates at a local site and spreads *via* systemic circulation (41, 42).

In the lung-kidney crosstalk, a close bidirectional relationship between alveolar and tubular damage because of toxic overproduction including cytokines and growth factors, as well as the release of damage-associated molecular patterns (DAMPs) from injured tissue in COVID-19 patients has been reported. When a cytokine storm occurs, the immune system may not be able to kill SARS-CoV-2, while it may kill large numbers of normal cells, damage tissues, organs, and finally become the cause of multiple organ failure (MOF). Cytokine storm can lead to severe ARDS. This type of inflammatory response may also harm the kidney. Many studies have emphasized the potential involvement of IFN pathways and viral trigger in podocyte and consequently glomerular injury. Podocyte dysregulation might be due to an infection-driven inflammatory response that releases cytokines or DAMPs. In turn, this product circulates and interacts with receptors on podocytes, which can be one of the important factors in the development of collapsing glomerulopathy (focal segmental glomerulosclerosis, FSGS) (43). In some settings, collapsing FSGS is closely related to the genetic expression of APOL1 G1 and/or G2 risk variants (which are observed in people of African American origin). SARS-CoV-2 infection may unmask APOL1-conferred genetic susceptibility to podocyte injury and development of collapsing FSGS (43).

In addition to being frequently associated with the cytokine storm, severe lung infections and/or ARDS often require prolonged mechanical ventilation. COVID-19-associated ARDS is often treated by increasing positive end-expiratory pressure (PEEP). During PEEP, there is an increase in intrathoracic pressure, which can lead to increased intrathoracic pressure, as well as increased renal venous pressure and reduced glomerular filtration rate (GFR). In addition, PEEP can also increase sympathetic tone (lead-

ing to secondary activation of RAAS), which also contributes to the development of AKI (11).

Moreover, patients who develop secondary infections (bacterial, fungal or viral) are at a higher risk of secondary sepsis-associated AKI. Sepsis is classically defined by marked hypotension that requires treatment with inotropic drugs. Therefore, in patients with sepsis, it is plausible that persistent hypotension and vasoconstriction induced by inotropics can participate in the development of renal medullary hypoxia, which is an additional insult to tubular cells and consequent ATN (44).

Rhabdomyolysis in the setting of COVID-19 can be a consequence of direct cytotoxic effect of SARS-CoV-2 on muscles, drug-induced or tissue hypoxia due to hypoxemia. Myoglobin demonstrates its toxicity by direct damage to renal tubular cells, renal vasoconstriction related to the hyperactivation of RAAS by hypoperfusion and intratubular cast formation, leading to ATN (45).

It is also important to note that a handful of studies have described COVID-19 patients presenting with primary cardiac symptoms referred to cardio-renal syndrome type 1 (46). Patients usually had myocarditis and stress-related cardiomyopathy due to respiratory failure and hypoxemia, but in some patients, concomitant heart and kidney failure may occur during sepsis (47). There is insufficient evidence to support direct viral infection of cardiomyocytes, but it should be remembered that maladaptive cytokine release directly affects cardiomyocytes and leads to endothelial cell dysfunction (48).

It is clear that the inflammatory process might contribute to the pathogenesis of COVID-19-associated MOF through the infiltration of infected tissue by host immune cells in order to contain viral replication. However, hyperactivation of these immune cells may lead to fibrosis, epithelial cell apoptosis and microvasculature damage participating in the pathogenesis of CKD.

Lymphopenia

The expression of ACE-2 in lymphocytes turns them into potential targets of SARS-CoV-2, which consequently results in cell death of both CD4+ and CD8+ T cells leading to an imbalance in both innate and acquired immune responses, neutrophils, macrophage hyperactivation, and delayed clearance of viruses (9, 11, 19). The consequent lymphopenia is most likely the result of a combined action of the inflammatory response (which leads to lymphocyte apoptosis), direct role of virus in lymphocyte death, or/and de-

struction of lymphatic organs by virus. The effects of SARS-CoV-2 on lymphocytic apoptosis, as well as on CD169+ macrophages present in lymph nodes and spleen, was proven at autopsy of patients who died from COVID-19 (33).

Dysregulation of complement system

The complement system, a significant component of native immunity, is critical to rapid response to infections. Its dysfunction leads to acute lung injury following a highly severe SARS-CoV-2 infection. COVID-19 activates the complement system *via* lectin and alternative pathways. The complement system produces anaphylatoxins (e.g., C3a and C5a), which bind to their specific receptors and stimulate the leukotrienes, histamine, and prostaglandins, which are responsible for the main symptoms of hypersensitivity (vasodilation, flushing, hypoxia, and hypotension). Assembly of complement C5b-9 through the alternative pathway in tubular apical brush border consequent to their accumulation in tubular lumen leads to tubulo-interstitial damage (36) (Figure 5). The complement activation and pro-coagulation pathways can stimulate one another.
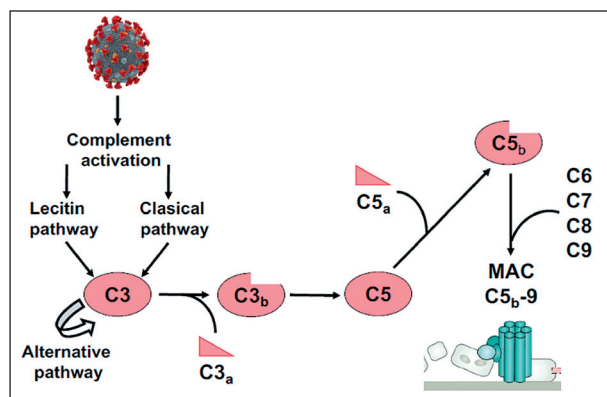

Fig. 5. *Effect of SARS-CoV-2 infection on the complement system.*

Complement cascade can be activated by three different pathways, the classic, lectin and alternative pathways. All three participate in creating the formation of C3 convertases that cleave C3, generating the pro-inflammatory peptide C3a and a large amount of C3b that opsonizes pathogens. The latter also forms the C5 convertase, which leads to release of the potent anaphylatoxin C5a, as well as the fragment C5b responsible for the formation of MAC C5b-9 on target cells, which is considered to be the terminal event of complement activation. Furthermore, complexes of SARS-CoV-2-specific antibodies and viral antigens might induce endothelial cell injury through activation of the C1 complex of the classic pathway and induction of ADC (60). Clinical insights into complement activation following SARS-CoV-2 infection are limited; there are indications that the downstream terminal phases of the complement cascade may contribute to endothelial cell injury, intravascular coagulation and thrombosis, leading to MOF in COVID-19 patients (49, 51, 60).

ADC, antibody-dependent cytotoxicity; MAC, membrane attack complex

Coagulopathy and microangiopathy

According to the latest data, the incidence of thrombotic complications in critically ill patients with COVID-19 is up to 49%, and it is accompanied by a significant mortality rate (>70%) (49). Critically ill patients are generally predisposed to thromboembolism, mainly due to a combination of favorable factors such as systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow. COVID-19-associated thrombotic complications seem to resemble systemic coagulopathies such as disseminated intravascular coagulation (DIC) or sepsis-induced coagulopathy (SIC). However, analysis of hematologic findings in COVID-19 patients indicates higher plasma levels of fibrinogen and D-dimers, as well as significantly elevated C-reactive protein(CRP) and ferritin values, associated with thrombocytopenia and relatively modest changes in prothrombin time (PT) and activated partial thromboplastin time (APTT) (19, 50, 51). Patients with COVID-19 have a specific procoagulant profile that manifests by a significant increase in D-dimer and fibrinogen levels, which significantly correlate with elevated IL-6 levels (52) and have good specificity and sensitivity in predicting the potential worse outcomes (53).

The rapid worsening of respiratory symptoms is accompanied by extremely marked and uncontrolled increase in pro-inflammatory cytokines (IL-2, IL-6, IL-7, IL-10, TNF-α, MCP-1, MIP-1A and IP-10), commonly referred to as the cytokine storm. Playing a critical role in acute inflammation, pro-inflammatory cytokines (especially IL-6) induce a wide spectrum of proteins including fibrinogen and thrombopoietin (54), activating complement pathway on endothelial cell membranes, mediating vascular endothelial growth factor (VEGF), signaling and promoting destabilization of vascular endothelial-cadherin resulting in increased vascular permeability (54, 55). Moreover, IL-6 can increase the level of tissue factor allowing the conversion of prothrombin to thrombin, and then permits fibrin clot formation. On the other hand, thrombin is able to induce IL-6 expression forming a reciprocal feedback. Therefore, in COVID-19 patients, acute uncontrolled inflammation and elevated IL-6 can affect coagulation and fibrinolysis in several ways and amplify hypercoagulability.

Otherwise, infection with SARS-CoV-2 directly or indirectly induces vascular endothelial dysfunction and thus increases the possibility of thrombosis. Due to COVID-CoV-2 infection mediated by ACE-2 and TMPRSS2, co-presence of the two proteins may underpin the tropism of virus attack. ACE-2 and TMPRSS2 are co-expressed in cells of the lung, heart, kidney, smooth muscle and neurons, but also in vas-

cular endothelium (50, 55, 56). Normally, in endothelial cells of the kidney, only ACE is expressed without detectable ACE-2 (57). However, ACE-2 expression can be changed in pathologic states or by some drugs (9), which may allow SARS-CoV-2 to infect directly renal endothelium (58). Recruitment of immune cells, either by direct viral infection of the vascular endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis. Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular

equilibrium towards more vasoconstriction with subsequent inflammation associated with tissue edema, organ ischemia, and a procoagulant state (59). SARS-CoV-2 infection facilitates the induction of endothelitis, apoptosis and pyroptosis in several organs as a direct consequence of viral involvement and of the host inflammatory response. COVID-19-endothelitis could explain the impaired systemic microcirculatory function in different vascular beds and their clinical sequels in patients with COVID-19 (19, 49-52, 59, 60) (Figure 6).
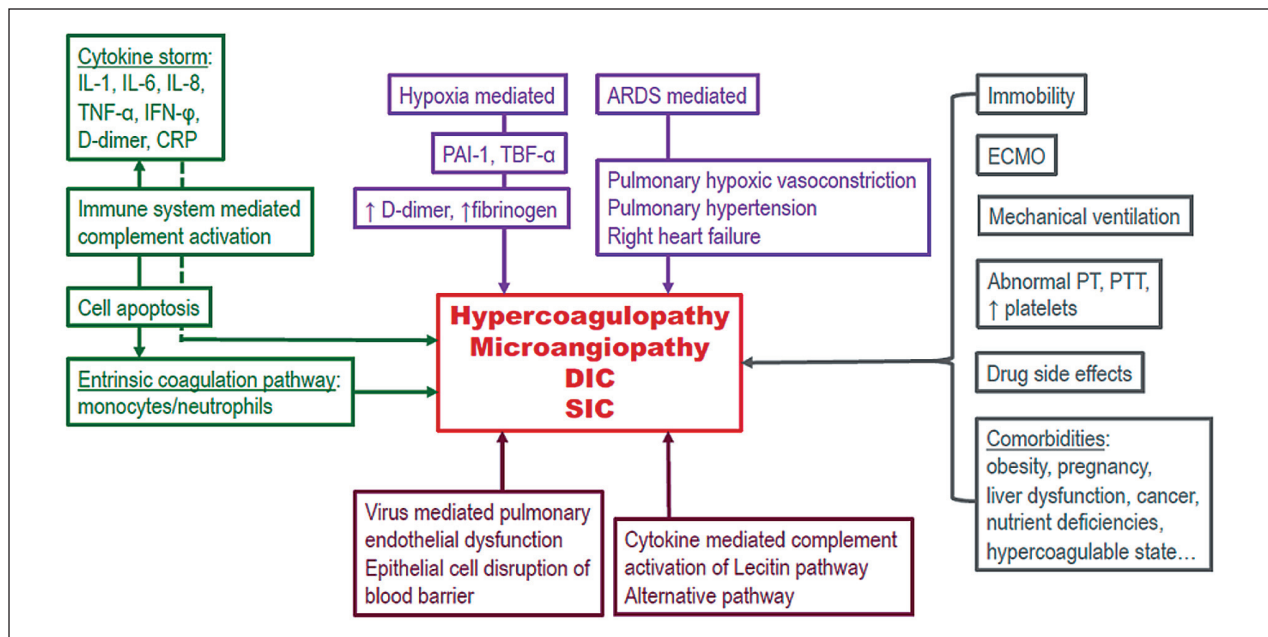

Fig. 6. *Multifactorial pathogenesis of coagulopathy in COVID-19.*

Hypoxia

Up to 35% of hospitalized patients with COVID-19 are treated in ICU, most commonly due to hypoxemic respiratory failure, with 29% to 91% of them requiring invasive mechanical ventilation (61). In addition to respiratory failure, hospitalized patients may develop AKI, mainly induced by ARDS (attributed to an infection driven inflammatory response that releases cytokines and viral products that can interact with podocytes and tubular cells and damage them) (62). The coexistence of hypoxia could further enhance the process and move the inflammatory response towards maladaptation. The involvement of the hypoxia-inducible factor (HIF) system, critical for inflammation and control of immune cell metabolism and function, is very likely. Hypoxia and inflammation are unequivocally linked, since hypoxia causes inflammation in exposed tissues and inflammation induces severe hypoxic response. The involvement of the HIF pathway during AKI effects a span from an increase of oxygen supply and adaptation to limited oxygen demand to a decrease in oxidative stress and regulation of inflam-

matory processes, stimulation of erythropoietin synthesis, improvement of mitochondrial metabolism, and reduced apoptosis (63).

Non-specific mechanisms

Non-specific mechanisms include older age, pre-existing comorbidities, hemodynamic alterations, hypovolemia, nosocomial sepsis, nephrotoxic drugs, angiographic contrast media, and high levels of PEEP in patients requiring mechanical ventilation.

As previously mentioned, mortality rates increase with age categories (e.g., mortality rate of 1.3% in the 50-59 age group, 3.6% in the 60-69 age group, 8% in the 70-79 age group, and 14.8% in the ≥80 age group), presence of CVD (10.5%), diabetes mellitus (7.3%), chronic pulmonary disease (6.3%), arterial hypertension (6%), neoplasms (5.6%) (4), and somewhat less frequently in the immune compromised status, smoking and obesity (64). According to data from the Italian Health Institute, the most common chronic diseases in patients who died from COVID-19 were arterial hypertension

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(70%), diabetes mellitus (31.7%), CKD (23.1%), atrial fibrillation (22.5%), chronic obstructive pulmonary disease (COPD) (18.1%), active neoplasm (16.8%), ischemic heart disease (16%), and obesity (10%). Approximately 47% of the patients who died suffered from 3 or more chronic diseases, 26% had 2 diseases, 26% had only one disease, and 1% did not suffer from any other disease (19). Patients with increased baseline serum creatinine (sCr) levels were more likely to develop AKI (11.9%) than patients with normal baseline values (4.0%). This means that, while renal complications are more likely in patients with pre-existing chronic renal failure, moderate-to-severe AKI can also be found in patients with normal sCr levels and these may represent a higher-risk subset of patients with ARDS (19). On hospital admission, a significant percentage of CKD patientspresented proteinuria and micro-hematuria (37). A higher incidence of proteinuria and micro-hematuria has been reported in patients with severe or critically ill COVID-19 pneumonia.

Due to these pre-existing comorbidities, patients are frequently treated with drugs that interfere with renal blood flowregulation, such as diuretics, ACE inhibitors, and other antihypertensive drugs. This could be of importance because many patients experienced prolonged fever, tachypnea and gastrointestinal symptoms (nausea, vomiting and diarrhea), which could lead to hypovolemia and subsequent pre-renal AKI. Cardiomyopathy and acute viral myocarditis can both contribute to renal venous congestion, hypotension, and renal hypo-perfusion, leading to reduction of GFR (34).

Similarly, critically ill patients might be exposed to nephrotoxic or/and hepatotoxic drugs as part of their clinical care, including antibiotics, lopinavir/ritonavir, remdesivir, tenofovir, nucleoside analogs, hydroxychloroquine sulfate and chloroquine phosphate (46, 65). Moreover, administration of angiographic contrast media also potentiates the risk of tubular toxicity (66).

Patients who develop secondary infections (regardless of whether they are viral, bacterial or fungal) are at a higher risk of secondary sepsis-associated AKI (11, 67).

Patients with severe COVID-19-associated ARDS and/or pneumonia are also at a high risk of AKI as a complication of mechanical ventilation. Specifically, COVID-19-associated ARDS is often treated by increasing PEEP, which leads to increased intra-thoracic pressure and can ultimately result in increased renal venous pressure and reduced GFR and urine output, which may be further amplified if intra-abdominal pressure is elevated (e.g., with fluid overload). In addition,

all forms of positive pressure ventilation can increase sympathetic tone, leading to secondary activation of the RAAS. Recently, it has been found that, in the early phase of COVID19 pneumonia, pulmonary mechanics may be different from traditional ARDS, characterized by normal compliance, low lung recruit ability, and without the need for very high PEEP or even deleterious effects of the latter (68). In other words, high and kidney-unfriendly levels of PEEP may not be required in the early phase of COVID-19 ARDS. Finally, inflammatory effects of invasive mechanical ventilation *per se*, especially when a non-protective strategy is applied, could also contribute to AKI (44, 46).

PATHOLOGY

In one of the first rapid autopsy series (postmortem interval was ≤6 h) performed on patients with COVID-19, all cases showed mild to severe AKI characterized by the loss of proximal tubular brush borders, vacuolar degeneration, pigmented casts in tubular lumens, pigmented granules within tubular cytoplasm, and frank epithelial cell necrosis (9) (Figure 7). In seven cases, there was evidence for glomerular ischemia, and fibrin thrombi within the glomerular capillary loops were found in three of them. In another retrospective study of 81 patients, 41 (50.6%) patients experienced AKI, and autopsy findings were consistent with acute tubular injury (ATI) (69). More recently, several kidney autopsy series from the USA and United Kingdom showed a high incidence of AKI with varying degrees of severity. The authors also report platelet-rich fibrin microthrombi in scattered peritubular capillaries and venules in most cases (36, 70-73).

No significant glomerular disease has been described in patients with COVID-19, with the exception of collapsing focal segmental glomerulosclerosis, which has been reported in approximately 40 patients (either alone or in combination with other pathologic findings in the kidneys) (37, 60), and seems to be associated with the presence of genetic risk variants of APOL1 G1 (74) (Figure 7). This pattern of injury is most strongly associated with viral infection and may increase the risk of interfe ron mediated podocyte injury due to COVID-19. Homozygosity for high-risk APOL1 allele is present in 14% of African Americans who collectively represent 12.9% of the USA population but account for an estimated 25.1% of USA COVID-19 deaths (75).

Microscopic changes associated with comorbid conditions such as hypertension and diabetes showed characteristic findings in glomeruli, which included nodular mesangial expansion and hyalinosis of arterioles (associated with diabetic nephropathy) and arteriosclerosis

of medium-sized arteries with ischemic glomeruli (9, 73). Finally, in addition to the possible contributors of kidney dysfunction during active COVID-19, preexistent CKD is a known independent risk factor to develop AKI. This could worsen the expected outcomes of these patients and may involve many pathophysiologic mechanisms dependent on comorbidities (33, 34).

In support of the hypothesis that SARS-CoV-2 exerts tropism in the kidney electron microscopy (EM) examination of autopsy samples from 26 patients who had died with COVID-19 demonstrated clusters of viral particles in the podocytes and tubular epithelium (9). Another study that involved microdissection of the tissue obtained on autopsy demonstrated detectable SARS-CoV-2 viral load in three of six deceased patients. In all positive samples, virus was detected in all kidney compartments examined, mostly targeting glo-

merular cells (76). In line with this finding, active viral replication in different tissues, including kidney tissue, was found in a subset of patients with COVID-19 (72), although it is still not clear whether this renal active replication contributes to viral burden in the body.

However, most analyses of kidney tissue used light microscopy, immunohistochemistry and/or EM, which cannot conclusively ascertain whether the identified particles are actually SARS-CoV-2 or merely viral-like structures. The identification of viral particles in kidney tissue by EM has been questioned given the resemblance of these particles to other cellular structures (e.g.,clathrin-coated vesicles) (77). The fact is that several studies were unable to confirm the presence of virus in the kidney, and that studies of SARS-CoV-2 in biologic fluids rarely showed viral shedding in the urine (78).
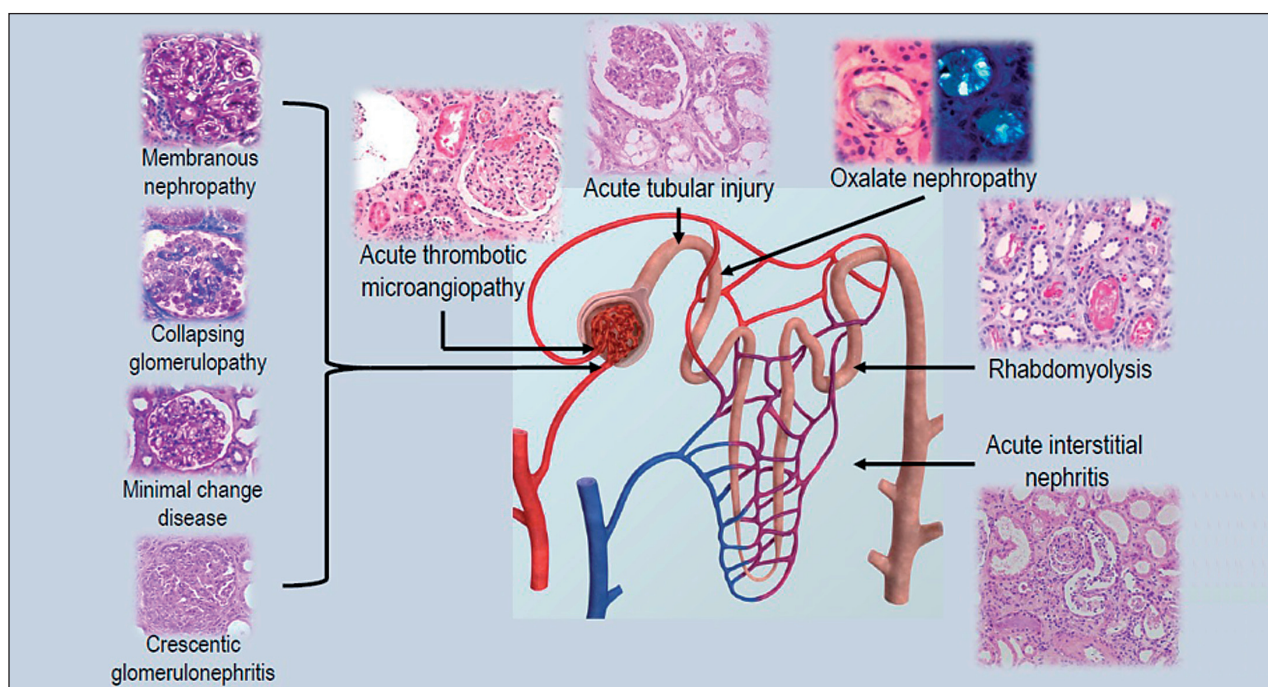

Fig. 7. *Histopathologic changes of the kidney that may be seen in COVID-19 patients with AKI.*

Evidence to date shows that the vast majority of AKI cases in patients with COVID-19 were related to ATI. This form of AKI has components of ischemia-reperfusion injury, direct inflammatory injury, coagulation and endothelial cell dysfunction, and apoptosis (34, 49, 53, 63). Tubular injury from rhabdomyolysis and severe hyperinflammation should be considered in the differential diagnosis of AKI in patients with COVID-19. The kidney autopsy samples from patients with COVID-19 showed prominent tubular injury, including the initial part of the proximal tubule, with loss of brush borders, epithelial cell necrosis, and collections of intraluminal debris. Interstitial disease was not as common as tubular injury (37). TMA has been described in patients with COVID-19, with the kidney biopsy showing diffuse cortical necrosis and widespread glomerular microthrombi. Collapsing glomerulopathy is the most common form of glomerular disease in association with COVID-19. The pathogenesis of COVID-19-associated collapsing glomerulopathy is unclear, but it has emerged as a distinct pathology associated with SARS-CoV-2 infection, which seems to specifically affect individuals of African ancestry who have high-risk APOL1 genotypes (G1/G1, G1/G2, or G2/G2) (37). Other glomerular diseases such as ANCA-associated vasculitis, anti-GBM disease, IgA vasculitis without nephropathy, membranous nephropathy and minimal change disease have been reported in patients with COVID-19. There are two possible explanations for the variety of glomerular diseases seen in patients with COVID-19: predilection for a specific glomerular pathology in these patients (SARS-CoV-2 acting as a 'second hit'); and these processes may be unrelated to SARS-CoV-2 (representing incidental findings).

AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; ATI, acute tubular injury; GBM, glomerular basement membrane; IgA, immunoglobulin A; TMA, thrombotic microangiopathy

DIAGNOSIS

The diagnosis of COVID-19 itself is based on the history of contact, clinical and laboratory evidence with hemogram, biochemical parameters, chest imaging with computerized tomography (CT), and virologic examination.

The clinical spectrum of SARS-COV-2 infection ranges from asymptomatic infection to critical and fatal illness. The proportion of infections that are asymptomatic is about 40%. According to the European Centre for Disease Prevention and Control, evidence from analyses of cases showed that up to 80% of patients with COVID-19 had mild disease, without pneumonia or with mild pneumonia, most of whom recovered spontaneously (79). Severe disease (e.g., with pneumonia and hypoxia) has been reported in 15% to 20% of symptomatic infections, and 6% become critically ill (79). It can occur in otherwise healthy individuals of any age, but predominantly occurs in adults with advanced age or certain underlying medical comorbidities (Table 1). Males, compared with females, have a disproportionately higher death rate (80).

The most frequent serious clinical manifestation of infection is pneumonia, which can be complicated with ARDS even in patients with initially mild symptoms. The range of associated symptoms was illustrated in a report of over 370,000 confirmed COVID-19 patients with known symptom status reported to the CDC in the USA, as follows: dry cough (50%), fever (43%), myalgia (36%), headache (34%), dyspnea (29%), sore throat (20%), diarrhea (19%), nausea/vomiting (12%), and loss of smell or taste, rhinorrhea and abdominal pain in fewer than 10% each (81). Other reported complications are thromboembolic events, including pulmonary or coronary embolism and stroke, encephalitis and encephalopathy, Guillain-Barre and Miller-Fischer syndrome, olfactory and taste dysfunction, conjunctivitis, cardiac injury, arrhythmias, liver and pancreas injury, intestinal inflammation, thyroid gland dysfunction, acute adrenal insufficiency, diffuse myalgia and rhabdomyolysis, lymphopenia, neutrophilia, DIC,testis dysfunction and spermatogonia, and cutaneous adverse events (82).

The rates of reported AKI vary considerably among studies (0.5% to 46%). Reports from the EU and USA describe a great burden of comorbid disease in association with higher rates of AKI (74). One possible explanation of the high prevalence of kidney involvement at hospital admission is that some of COVID-19 patients may have already had a history of CKD. Such patients tend to have a pro-inflammatory state with functional defects in their immune system, and are at a higher risk of upper respiratory tract infection, pneu-

monia and ARDS. In ARDS, the severity of illness, patient age and presence of diabetes and/or hypertension are all risk factors for acute-on-chronic kidney injury. Interestingly, a recent prospective study including 701 patients with moderate or severe COVID-19 showed that 43.9% exhibited proteinuria and 26.7% hematuria at hospital admission, while 13% presented elevated levels of sCr, blood urea nitrogen (BUN) or both (20). During hospitalization, AKI occurred in 5.1% of COVID-19 patients. Patients with different degrees of proteinuria and hematuria had a significantly higher risk of in-hospital death after adjusting for age, gender, comorbidity, disease severity and leukocyte count (20, 33).

Polymerase chain reaction and serology

Reverse transcription polymerase chain reaction (PCR) based SARS-CoV-2 RNA detection from respiratory samples (e.g., nasopharynx) is the standard for diagnosis. The sensitivity of testing varies with the timing of testing relative to exposure. One modeling study estimated sensitivity at 33% four days after exposure, 62% on the day of symptom onset, and 80% three days after symptom onset (83). Factors contributing to false-negative test results include the inadequacy of the specimen collection technique, time from exposure, and specimen source. Lower respiratory samples such as broncho-alveolar lavage fluid are more sensitive than upper respiratory samples (84).

Wang *et al*. examined the credibility of PCR among 1070 specimens collected from 205 patients with COVID-19 and found that broncho-alveolar lavage fluid specimens had the highest positive rates of SARS-CoV-2 PCR test results (93%), followed by sputum (72%), nasal swabs (63%), and pharyngeal swabs (32%) (83). SARS-CoV-2 can also be detected in feces, while the finding in the urine is still questionable.Saliva may be an alternative specimen source, but requires further validation.

Several serologic tests can also aid in the diagnosis and measurement of responses to novel vaccines. However, the presence of antibodies may not confer immunity because not all antibodies produced in response to infection are neutralizing. IgM antibodies are detectable within 5 days of infection, with higher IgM levels during weeks 2 to 3 of illness, while an IgG response may be seen approximately 14 days after symptom onset (84, 85). Higher antibody titers occur with more severe disease. Available serologic assays include point-of-care assays and high throughput enzyme immunoassays (85).

Laboratory features

Based on the analysis of 19 studies involving 2874 patients with SARS-CoV-2 infection, of whom 88% were hospitalized, a typical profile of laboratory abnormalities seen in COVID-19 was made. Serum CRP, lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated inapproximately 60%, 50%, 25% and 33% of patients, respectively (86). Approximately 75% of patients had low serum albumin, and the most common hematologic abnormality was lymphopenia, which was present in up to 83% of hospitalized patients with COVID-19 (4). In conjunction with coagulopathy, modest prolongation of prothrombin times, mild thrombocytopenia and elevated D-dimer values have been reported (49). More severe laboratory abnormalities have been associated with more severe infection. However, most of these laboratory characteristics are nonspecific and common in pneumonia. Patients with COVID-19 AKI have also been reported to have higher levels of systemic markers of inflammation, particularly CRP, ferritin, pro-calcitonin and LDH than patients with COVID-19 and normal kidney function (11).

The standard assessment and staging of AKI is still based on sCr levels and hourly urine output (Kidney Disease Improving Global Outcomes /KDIGO/AKI guideline) (87). The lack of sCr measurements prior to hospital admission often impedes the ability to identify underlying CKD and creates challengers for the reliable detection and staging of AKI, emphasizing the need to define baseline sCr clearly. To improve understanding of the temporal nature of COVID-19 AKI, physicians must correlate the timing of AKI with COVID-19 symptom onset confirmation of SARS-CoV-2 infection, hospitalization, disease severity, and level of care when reporting AKI rates (11).

Although urine volume is reported infrequently, 70% of patients have low urinary sodium concentrations at the time of AKI, and the majority are anuric at renal replacement therapy (RRT) initiation (3, 11). Urine analysis is frequently abnormal in patients with COVID-19 and could be used to characterize AKI in these patients. Hirsch *et al.* report that among 32% of hospitalized COVID-19 patients in whom urine analysis was available, 42.1% had significant proteinuria, with hematuria and leukocyturia in 40.9% and 36.5%, respectively (88). Examination of urine sediment can be an effective tool in clinical practice in which more than one possible cause of AKI may exist that could affect medical management (e.g., to distinguish pre-renal AKI from ATN).

Viral factors

Patients with severe disease have also been reported to have higher viral RNA levels in respiratory specimens than those with milder disease, although some studies found no association between respiratory viral RNA levels and disease severity. Detection of viral RNA in the blood has been associated with severe disease, including organ damage (e.g., lung, heart, and kidney), coagulopathy, and mortality (58).

Imaging

The characteristic chest CT imaging abnormalities in COVID-19 are diffuse, peripheral ground-glass opacities with ill-defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura (85). Some patients admitted to the hospital with PCR-confirmed SARS-CoV-2 infection have normal CT imaging findings, whereas in other patients, abnormal chest CT imaging findings compatible with COVID-19 occur days before detection of SARS-CoV-2 RNA. Rapid evolution of abnormalities can occur in the first two weeks of symptom onset, after which they subside gradually.Chest CT scan remains the most sensitive imaging modality in initial diagnosis and management of suspected and confirmed patients with COVID-19 (89). Other diagnostic imaging modalities (e.g., lung ultrasound, chest x-ray, or positron emission topography/ computed tomography (PET/CT) scan) could add value in evaluating disease progression and monitoring critically ill patients with COVID-19 (90).

The diagnostic criteria and AKI staging is not different from AKI in other situations (91-95).

MANAGEMENT OF ACUTE KIDNEY INJURY

Given the high incidence of kidney involvement in SARS-CoV-2 infection and the lack of specific treatment options, the care strategy for patients with COVID-19 in the ICU remains largely supportive.

In current circumstances, it is essential to reinforce the need for close collaboration between intensivists and nephrologists. The nephrologist should be contacted even in the case of a patient with relatively small renal impairment, since its involvement in ICU is not limited to AKI. Kidney involvement in COVID-19 patients may precede, be concomitant, or follow other organ system failure. This situation can require fully competent and trained personnel to implement all therapeutic options for critically ill patients. Therefore, intensivists and nephrologists should discuss all diagnostic and therapeutic possibilities in individual pa-

tients, taking into account hemodynamic parameters, volume status, electrolyte and acid-base disturbances, degree of kidney injury, comorbid conditions, and adjustment of drug doses. This is especially true for patients with COVID-19 who, according to the KDIGO classification of AKI, meet the criteria for stage 2 renal impairment. Patients classified as stage 3 have a high probability of requiring RRT, which requires an urgent call to the nephrologist team.

Non-dialytic management

All patients with AKI need careful assessment of hemodynamic and volume status using vital signs and physical examination. Critically ill patients may benefit from more invasive hemodynamic monitoring (arterial line, central venous pressure, or cardiac output monitoring). Measurement of fractional excretion of sodium and urea in urine may be helpful in diagnosing decreased kidney perfusion in oligo-anuric patients. However, the utility of these diagnostic methods tends to be more limited in critically ill adults, likely as a result of coexisting pre- and intra-renal disease. Urinary microscopy for renal tubular epithelial cells and granular casts may be helpful to make the concomitant diagnosis of ATN, which is the most common cause of AKI occurring in the hospital.

Measures to prevent AKI include optimization of volume status and avoidance of nephrotoxic medications. Volume depletion at admission might be common in patients with COVID-19, as they typically present with fever and pre-hospital fluid resuscitation is rarely performed. Crystalloids are preferred over colloids for most patients, and hydroxyethyl starches should be avoided. Patients with reduced renal blood flow who can augment their cardiac output by expansion of their intravascular volume would benefit from fluid resuscitation (96). Balanced crystalloids should be considered in patients with hypotension, severe systemic inflammatory response, and elevated sCr on presentation. After significant volume resuscitation, even if patients remain volume responsive, vasopressor support should be considered to avoid markedly positive fluid balance (97). Escalating dosages of intravenous loop diuretics in patients with volume overload, intravenous sodium bicarbonate solution in patients with severe metabolic acidosis, and use of rapid acting potassium binders (e.g., sodium zirconium cyclosilicate) for hyperkalemia can potentially delay RRT. The potential renal benefit in glucose control was demonstrated, but it is certainly necessary to avoid hypo- and hyperglycemia (both are associated with increased morbidity and mortality in a variety of clinical scenarios) (98) (Figure 8).

High risk	AKI stage 1	AKI stage 2	AKI stage 3
Standard of care to prevent and manage multiorgan failure			
Consider dynamic hemodynamic monitoring			
Individualize fluid management, avoid saline unless specific indication			
Monitor serum creatinine and urine output			
Correct hypoglycemia			
Avoid nephrotoxic agents when possible			
Consider AKI risk in selecting ventilator strategies			
Consider alternatives to radiocontrast if possible without delaying urgent imaging			
	Diagnostic workup		
		Consider altered pharmacokinetics	
		Consider renal replacement therapy	
			Avoid subclavian access

Fig. 8. *Stage-based management of COVID-19 acute kidney injury (AKI).*

The pathogenesis of AKI in patients with COVID-19 involves direct viral effects, indirect effects and sequels of disease management. There is no specific evidence to suggest that COVID-19 AKI should be managed differently from other causes of AKI in critically ill patients. However, all features of the underlying disease, as well as associated chronic diseases should be considered during the treatment of patients with COVID-19 AKI.

Renal replacement therapy

Timing of RRT initiation in AKI is still controversial because multicenter studies in patients with sepsis and other causes did not clearly demonstrate benefit with early initiation of dialysis (99). Currently, there are no data to support early initiation of RRT in patients with COVID-19-associated AKI. Initiation of RRT should not be based on the stage of AKI, but should be considered when life-threatening complications of AKI (e.g., volume overload, acute pulmonary edema, severe metabolic acidosis /pH <7.1/, severe hyperkaliemia /K >6.5 mmol/L/) cannot be treated with conservative measures.

Furthermore, it is considered in patients with severe COVID-19 who developed AKI of KDIGO standard grade ≥2, particularly with sepsis, as well as in patients with severe systemic inflammatory response when the serum inflammatory mediator levels reach more than 5 times the upper limit of normal or increase more than one time within 24 hours (100).

The basic principles of RRT for patients with severe COVID-19 include the following: 1) removal of metabolic products, various inflammatory mediators and balancing of the immune homeostasis; 2) correction of electrolyte and acid-base balance disorders to maintain internal environment stability; 3) regulation of volume and correction of fluid overload to help maintain hemodynamic stability in critically ill patients; 4) control of high fever; and 5) combined RRT treatment with extracorporeal organ support (ECOS).

Prescribing blood purification treatment for patients with severe COVID-19 must be goal-oriented. The specific contents include the choice of blood purification treatment mode, vascular access, selection of blood purification filters, selection of anticoagulant, treatment dose, and initial parameter settings (Figure 9). In the face of shortage of RRT machines and medical staff capable to provide therapy, institutions had to adjust standard treatment practice. Higher dialysate flow rates were used in continuous renal replacement therapy (CRRT) modalities when treatment time was decreased. In order to place hemodialysis (HD), CRRTor HT machines outside patient rooms and minimize exposure to SARS-CoV-2 for physicians and nurses, an additional extension tubing was used. However, extension tubing increases circuit length and thus carries a risk of blood loss, hypothermia, and thrombosis. Therefore, appropriate warming systems should be implemented. Video monitors can help nurses supervise dialysis process without entering patient room. Isolated slow continuous ultrafiltration (SCUF) sessions were implemented in-between treatments for volume management. IHD treatment time and frequency were decreased if metabolic derangements and volume status would permit.
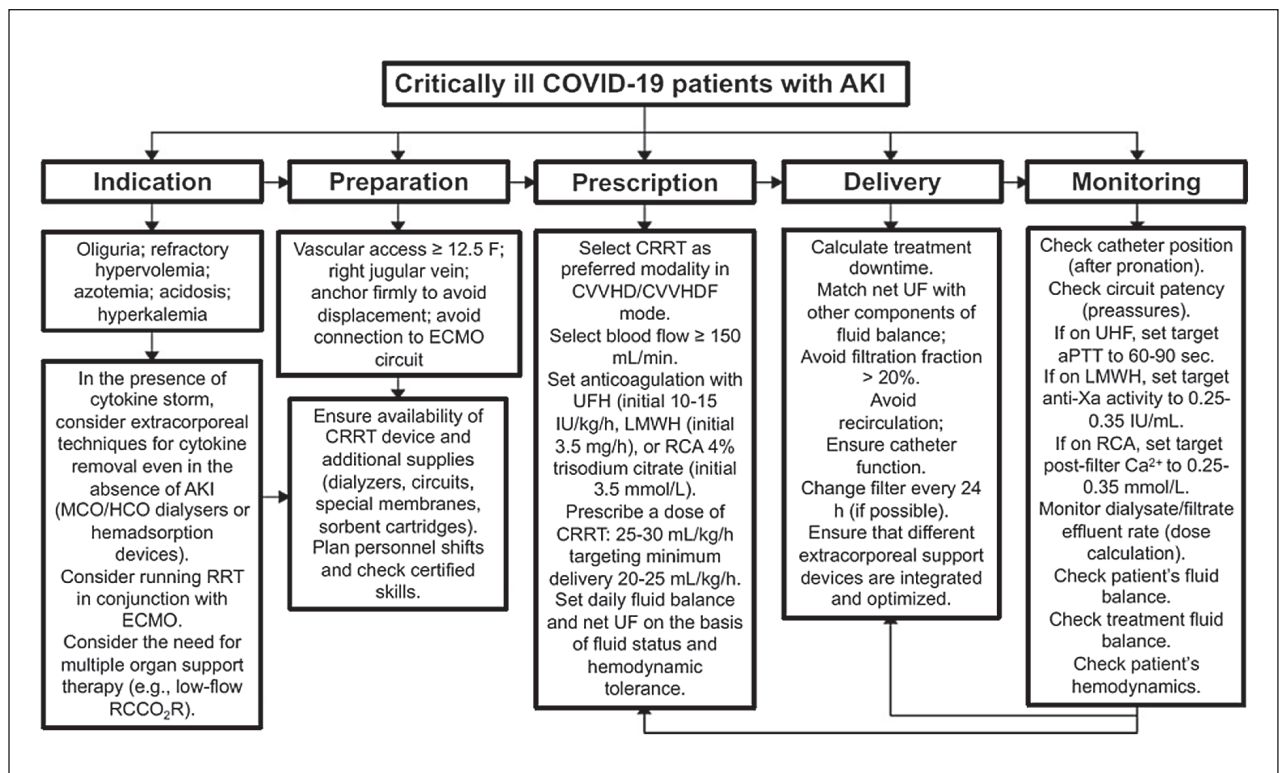

Fig. 9. *Prescribing blood purification treatment for critically ill COVID-19 patients with acute kidney injury.*

Continuous renal replacement therapy

In COVID-19 patients with refractory fluid overload and/or marked hemodynamic instability, there is a strong physiologic rationale for initial support with CRRT to offer greater hemodynamic tolerance, consistency in ultrafiltration (UF), and less osmotic and metabolic fluctuations (87, 99). Depending on the mechanism of clearance, CRRT can be delivered as continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemofiltration (CVVH), and continuous veno-venous hemo-diafiltration (CV-VHDF). CVVHDF (convective clearance) is not superior to CVVHD (diffusive clearance). In fact, CV-VHDF may be associated with higher rates of filter clotting due to higher filtration fraction.

When the main purpose is to remove inflammatory mediators in patients with severe COVID-19 and cytokine storm, it may be recommended to use high volume hemofiltration (HVHF), high cutoff molecular weight hemofiltration, or continuous plasma filtration absorption (CPFA) (100, 101). In patients with severe SARS-CoV-2 infection combined with simple volume overload and acute pulmonary edema, slow continuous ultrafiltration (SCUF) is recommended (99). When severe COVID-19 coexists with ARDS, CRRT with extracorporeal membrane oxygenation (ECMO), or extracorporeal CO_2 removal (ECC_2R) can be recommended.

Prolonged intermittent hemodialysis (hybrid therapy)

Alternatively, forms of prolonged (hybrid therapy, HT) and conventional intermittent RRT have an important complementary role in the support of critically ill patients with COVID-19 infection. These patients may frequently require mobilization and pronation to improve pulmonary gas exchange. In these circumstances, treatments of 8 to 12 hours may represent a good compromise between CRRT and intermittent hemodialysis (IHD) (102).

Hybrid dialysis modality is increasingly used in critically ill patients since it allows to maintain acceptable hemodynamic stability and to overcome the increased clotting risk of the extracorporeal circuit, especially when regional citrate anticoagulation (RCA) protocols are applied. HT can be performed either with CRRT, IHD or hybrid therapy device (GENIUS®, Fresenius Medical Care, Bad Homburg, Germany), providing adequate daily treatment dose in less time compared with CRRT, thus optimizing the often limited available resources in the overcrowded clinical context of SARS-CoV-2 in the ICUs. Notably, given the mainly diffusive mechanism of solute transport, HT is associated with lower stress on both hemofilter and blood cells as compared to convective RRT modalities. Finally, RCA,

as compared with heparin-based protocols, does not further increase the already high hemorrhagic risk of patients with AKI. Based on these premises, Di Mario *et al.* performed a pilot study on the clinical management of critically ill patients with COVID-19 associated AKI who underwent HT with a simplified RCA protocol. Low circuit clotting rates were observed and adequate RRT duration was achieved in most cases, without any relevant metabolic complication or worsening of hemodynamic status (103).

Intermittent hemodialysis

Intermittent hemodialysis is a traditional modality for providing RRT in hemodynamically stable patients. It may be employed as a second-line option for COVID-19 patients with AKI. In patients with ARDS who require prone positioning, IHD needs a coordinated protocol to provide adequate ventilator support in the prone position and HD therapy in the supine position. A synchronized team approach should be implemented to coordinate and maintain the safety of vascular access during prone positioning (104).

Potential practice change in a setting of COVID-19 AKI surge is to decrease treatment time and frequency (e.g., two times *per* week) to optimize medical supplies and decrease medical staff exposure to SARS-CoV-2 infection (105). Consideration for patient safety should be paramount when implementing any resource conservation and exposure reduction measures. Patients should be carefully monitored for manifestations of inadequate dialysis.

Providing IHD to a patient with COVID-19 may require one-on-one dialysis nursing support, whether in the ICU or on the general hospital floor. Strategies proposed to conserve human and material resources, and decreased exposure includes decreasing duration of treatments, decreasing frequency of IHD to twice a week, and tele-monitoring (e.g., use of monitors or tablets to visualize patients from outside the room).

Peritoneal dialysis

Experiences from resource-limited countries have shown adequate metabolic and fluid control with acute peritoneal dialysis (PD) in AKI. Under usual circumstances, acute PD is used in adult patients with AKI because regulation of UF and metabolic control is superior with CRRT in patients who are hemodynamically unstable. However, owing to acute surge during the pandemic, acute PD and continuous automated peritoneal dialysis (CAPD) have been implemented in hospitals because of shortage in extracorporeal RRT consumables, fluids, and nursing. Bedside catheter placement of a cuffed PD catheter is preferred for critically ill patients.

In the COVID-19 crisis, CAPD would be a preferred modality because it minimizes the number of connections and disconnections. Automated cycler use and extension tubing to keep device outside the patient room may limit exposure of healthcare staff. An average-sized adult can usually tolerate 2-L exchanges, but reduced volume should be considered for the initial few exchanges to decrease the risk of peri-catheter leaks. To maximize efficiency of acute PD, an exchange time of 1-2 hours should be used. Assuming a 2-L exchange volume with 60-minute exchange time, UF of about 1.2-3.6 L/day can be achieved with 1.5%, 2.4-7.2 L/day with 2.5%, and 7.2-9.6 L/day with 4.25%. As such, for patients with severe pulmonary edema, initial rapid in-out exchanges using 4.25% can be considered (105). The recommendation of weekly Kt/V urea is 3.5 (which provides results comparable to those of daily HD). This dose may not be necessary for all patients, and a lower goal of weekly Kt/V about 2.1 may be acceptable (106, 107).

Peritoneal dialysis can increase intra-abdominal pressure, interfere with respiratory mechanics, and may theoretically worsen respiratory failure, particularly in mechanically ventilated patients. Therefore, expert recommendations mention that PD can be started early, before patients develop ARDS. However, when ARDS occurs, PD should not be used as the first option for RRT (except when other options such as IHD, HT and CRRT are not available) (106). In patients requiring prone positioning, PD may not be feasible.

Vascular access

Appropriate central venous access is imperative to provide sufficient blood flows during RRT. Hemodialysis catheter length for adults according to the vein puncture site (15-18 cm for right internal jugular, 18-20 cm for left internal jugular, 24-28 cm for femoral, 15-18 cm for right subclavian, 20-24 cm for left subclavian) and location must be carefully selected, as inappropriate catheter length can lead to inadequate blood flow that leads to increased filter clotting. The right internal jugular vein is the preferred access for RRT as it offers a direct path for the catheter tip to be placed at the junction of the superior vena cava and right atrium. There is some controversy whether the second choice should be the left internal jugular or the femoral vein. The femoral vein site may be associated with a higher risk of infections and blood flow may be affected in patients who need to be in the prone position for ventilation. The left internal jugular vein can provide inadequate blood flow (especially when shorter catheters are inadvertently placed) (108). Vascular access *via* the subclavian vein is not recommended. If possible, ultrasound guidance should be used when placing the central venous catheters.

Blood purification filters

The choice of filter depends on the method of blood purification. Filters with synthetic biocompatible membrane and a high ultrafiltration coefficient are generally used to perform CRRT. Filters with absorption properties (e.g., oXiris membrane, AN69ST) or hemofilters with super high-flux (SHF) or high cutoff (HCO) membranes should be selected to remove inflammatory mediators. The SHF/HCO membranes also restore immune cell function, attenuate hemodynamic instability, decrease plasma IL-6 levels, and eliminate larger late-phase inflammatory mediators with acceptable albumin losses (109).

When performing plasma replacement and blood/plasma absorption, the corresponding plasma filter, blood perfusion device, or absorber can be selected depending on the procedure to be applied.

Anticoagulation

There is growing evidence for endothelial activation causing a hypercoagulable state, leading to a higher incidence of thrombotic complications in patients with COVID-19 (49-52). In addition to deep vein thrombosis, pulmonary embolism and ischemic stroke, clotting of extracorporeal circuits is a major concern, as it decreases dialysis filter and extracorporeal circuit lifespan. Despite disparities in outcome among individual anticoagulation strategies, it is an undisputed fact that circuits without anticoagulation tend to perform poorly in COVID-19 patients with AKI, when compared to anticoagulated systems. The bleeding risk of each individual patient needs to be considered prior and during the implementation of any anticoagulation options summarized in Table 2, given that anticoagulation (especially when systemic) may increase the propensity for bleeding (105, 110).

Table 2.
Anticoagulation strategies for kidney replacement therapy in COVID-19 patients with acute kidney injury

Anticoagulant	Dose	Remarks
Pre-filter unfractionated heparin	<u>Loading dose</u>: 2.000-5.000 units <u>Maintenance</u>: 10-15 units/kg/h <u>Check PTT</u>: 2-4 h after initiation <u>Target</u>: 5-s increase	Anticoagulation is intended for the circuit, not for the patient Higher risk of circuit clotting in high-risk patients
Systemic unfractionated heparin	<u>Loading dose</u>: 50-80 units/kg <u>Maintenance</u>: continuous drip at 18-20 units/kg/h <u>Target PTT</u>: 80-100	Protocols may vary. Higher risk of bleeding when comparted to pre-filter heparin Increased risk of HIT and heparin resistance Short half-life
Systemic low-molecular-weight heparin	Dose may be variable, and single pre-dialysis dose may be sufficient	Risk of accumulation in kidney failure Monitoring requires anti-Factor Xa Reduced risk of HIT
Regional citrate anticoagulation	No universal protocol	Requires institutional commitment Better safety profile than heparin Risk of overdose, metabolic acidosis, and hypocalcemia Increased monitoring of iCa and titration of CaCl
Argatroban	0.5 mcg/kg/min if normal liver function 0.2-0.25 mcg/kg/min in patients with liver dysfunction <u>Target PTT</u>: two times the normal value and titrate based on institutional protocol	Variable institutional protocols Dose different for those with and without liver dysfunction Use if HIT

PTT, partial thromboplastin time; HIT, heparin induced thrombocytopenia; iCa, ionized calcium; CaCl, calcium chloride

Renal replacement therapy dose

The dose of RRT should be based on KDIGO recommendations and adjusted in response to changes in clinical, physiologic and/or metabolic status (87). The standard recommended dose for CRRT is delivered effluent flow rate of 20-25 mL/kg/h (prescribed dose of 25-30 mL/kg/h). The minimum weekly dose of IHD and HT is three times *per* week (alternative days). Interruption of prolonged RRT modality (CRRT, IHD or HT) sessions due to circuit clotting can have a substantial impact on the actual delivered dose and the dose may therefore need to be adjusted to account for this disruption. Acute PD might also be an effective option for patients who are unable to receive anticoagulants. The recommendation of weekly Kt/V urea is 3.5, but a lower goal of weekly Kt/V about 2.1 may be acceptable (11).

In case of the increased need for RRT or shortages of CRRT, IHD or HT devices, as well as shortages of consumable medical materials, it is possible to reduce the dose of dialysis. In that case, it is necessary to make appropriate adjustments in fluid removal targets and RRT dose to achieve appropriate fluid balance targets and metabolic control (e.g., increase ineffluent dose).

Extracorporeal organ support

The majority of patients with COVID-19 admitted to the ICU have bilateral pneumonia with single-organ failure and consequent refractory hypoxemia. Other patients with SARS-CoV-2 infection suffer from significant derangement of the immune system, producing multisystem inflammatory syndrome, ARDS, sepsis, condition similar to DIC, rhabdomyolysis and damage to or failure of various organ systems. Severe AKI occurs mostly in the context of MOF. In such circumstances, RRT alone is usually not enough, but the function of several organs needs to be replaced at the same time. Extracorporeal organ support encompasses all forms of organ support by an extracorporeal circuit (e.g., RRT, ECMO, ECC_2R, hemoperfusion, high-volume HVHF, CPFA, therapeutic plasma exchange /TPE/, various blood purification devices, ventricular assist devices and extracorporeal liver support system) (99-101). In COVID-19 patients, recent platforms allow circuit adjustment to perform different ECOS techniques besides RRT.

Lung-protective ventilation and ECOS are the current standard of care for COVID-19 patients with ARDS. This approach can limit ventilation-induced lung injury, but it may be associated with respiratory acidosis and insufficient correction of hypercapnia (44). The technique of $ECCO_2R$ has been introduced for hypercapnic respiratory failure not requiring significant oxygen support. The effective amount of extracorporeal CO_2 removal from patients depends on blood flow. Studies have shown progressive CO_2 removal until blood flow of 800-1,000 mL/min where the ceiling is reached. Low blood flow $ECCO_2R$ devices (<0.5 L/min) achieve partial CO_2 removal (111). To date, several $ECCO_2R$ devices are available that can be used in conjunction with RRT hardware using variable blood flows. This may be particularly appealing in patients with ARDS and concomitant AKI, where compensatory renal mechanisms are less effective in regulating acid-base homeostasis during hypercapnic acidosis (111).

Lung and cardiac injury with COVID-19 can lead to hypoxia and decreased kidney perfusion, which in turn can lead to kidney medullary hypoxia and cardio-renal syndrome. Therefore, treatment of MOF in critically ill patients with COVID-19 may necessitate ECOS, including RRT, ECMO, and a left ventricular assist device (LVAD). Supporting the heart and lung in these conditions using LVAD and ECMO can potentially help with kidney perfusion (104). Direct hemoperfusion using a macro-porous sorbent has been suggested as a treatment to adsorb and remove circulating cytokines and prevent cytokine release syndrome (CRS)-induced end-organ damage (112). All these modalities can be used in conjunction with CRRT to help manage the MOF commonly seen in critically ill patients with COVID-19 (Table 3, Figure 10).

Table 3.
Pathophysiology of AKI and treatment strategies in COVID-19

Etiology	Pathophysiology	Treatment strategy
Systemic effects		
Positive fluid balance	Renal compartment syndrome	Diuretics, SCUF
Endothelial damage, third-space fluid loss, hypotension	Renal hypoperfusion	Fluid expansion, vasopressors
Rhabdomyolysis	Tubular toxicity	CRRT using MCO or HCO membrane
Endotoxins	Septic AKI	Endotoxin removal using polystyrene fibers functionalized with polymyxin-B
Cytokine overproduction		
Cytokine release syndrome	Direct cytokine injury	Cytokine removal using various approaches: high dose CRRT with MCO and HCO membranes; CRRT with hollow fiber filters with adsorptive properties; direct hemoperfusion using a neutro-microporous sorbent; plasma adsorptiom on resin after separation from whole blood
Increased cytokine generation owing to ECMO, invasive mechanical ventilation and/or CRRT		
Hemophagotic syndrome		
Organ crosstalk		
Viral myocarditis and/or cardiomyopathy	Cardiorenal syndrome type 1	LVAD, arteriovenous ECMO
Alveolar damage	Renal medullary hypoxia	
Rhabdomyolysis	Tubular toxicity	CRRT using MCO or HCO membrane
High peak airway pressure and intra-abdominal hypertension	Renal compartment syndrome	Venovenous ECMO, extracorporeal CO_2 removal, CRRT

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HCO, high cut-off; LVAD, left ventricular assist device; MCO, medium cut-off

Although bacterial sepsis is not a common feature in COVID-19 patients, the immune response to SARS-CoV-2 may lead in some patients to severe CRS with consequent organ dysfunction or even MOF. Thus, life-threatening organ dysfunction caused by a dysregulated host response to infection depends not only on systemic inflammation due to innate immunity but also on the possible severe immunosuppression due to adaptive immunity (111). In case of COVID-19 infection and CRS, with superimposed gram-negative bacterial infections, hemoperfusion with polymyxin-B (PMX-HP, Toraymyxin, Japan) should be used for two consecutive days, followed by the methods of cytokine adsorption (CytoSorb, Cytosorbents, USA or oXiris, Baxter, USA), and if organ support is required, CRRT should be implemented in conjunction or afterwards (105, 111-113).

Cascade hemofiltration, HVHF, TPE, hemoperfusion, CPFA, high-adsorption hemofiltration, as well as HCO or medium cut-off (MCO) membranes have been proposed based on the pathophysiologic rationale of cytokine and chemical mediator removal and/or modulation of the inflammatory response to sepsis. This removal may result in a decrease of the peaks of cytokine concentrations and/or modification of the cytokine/chemokine ratio from the tissues to the blood, positively affecting the leukocyte trafficking. However, it should be taken into account that patients are not homogeneous in terms of their inflammatory phenotype and have widely varying levels of cytokines in their blood. Therefore, these procedures may not help all patients. Unfortunately, specific criteria have not yet been defined.

It has been suggested that the use of ECOS (e.g., invasive mechanical ventilation and ECMO) may further stimulate inflammatory response involved in the lung-kidney and heart-kidney interaction. Consequently, more than 70% of patients receiving ECMO develop AKI, and the majority are treated with RRT (114). There are multiple reasons for AKI in patients who need ECMO; the exact contribution from ECMO support *per se* is unknown. The potential contributing factors may be inflammatory reactions in response to contact with artificial membrane, hemolysis and iatrogenic plaque rupture during arterial cannulation, and cannula malposition leading to kidney congestion (111). Therefore, the interaction between different types of ECOS support needs to be considered.
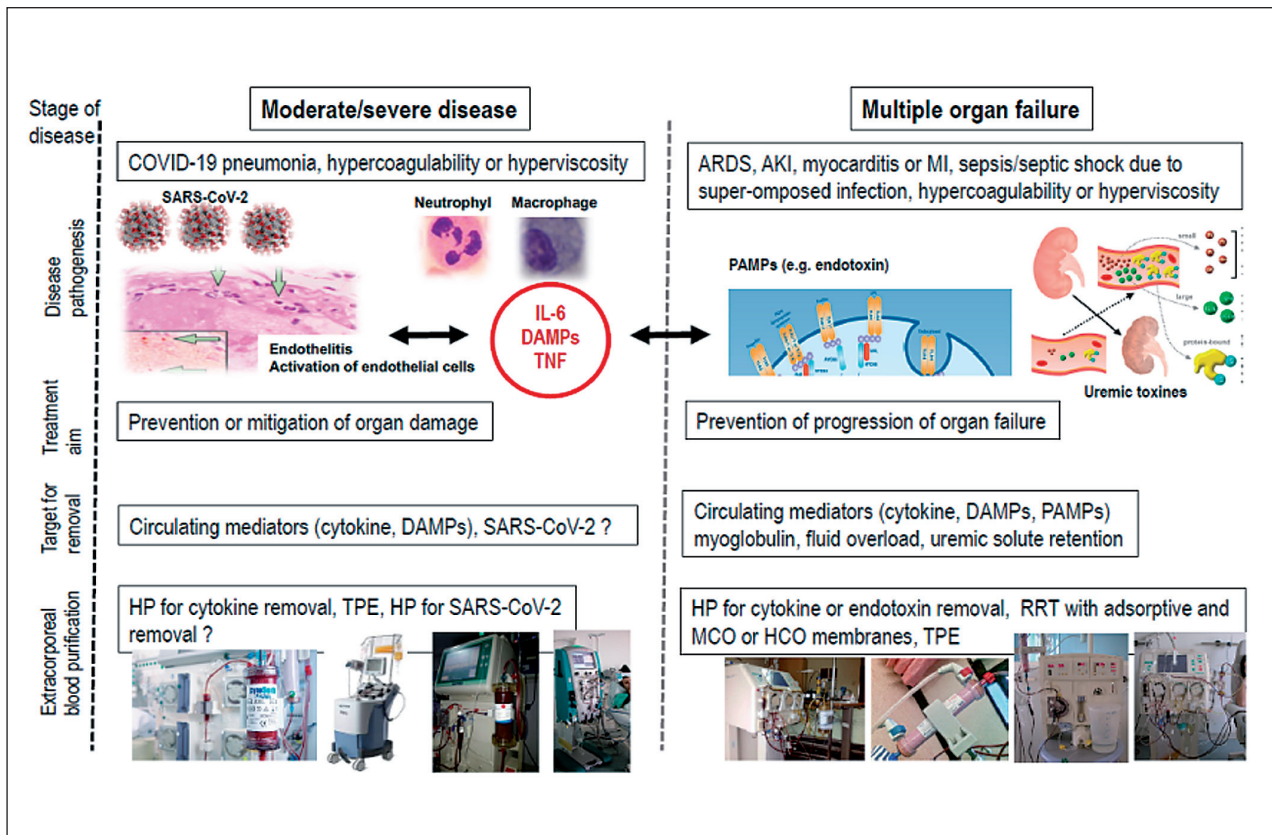
Fig. 10. *Potential extracorporeal blood purification treatment optionsbased on underlying COVID-19 pathophysiology.*

Extracorporeal blood purification (EBP) has been proposed as a possible adjuvant therapy for critically ill patients with CO-VID-19, considering that removal of circulating immunomodulatory factors that might contribute to disease processes and/or development of MOF, might improve outcomes. MOF in COVID-19 might result from propagation of an uncontrolled host immune response involving the release of various immune mediators such as cytokines, DAMPs and PAMPs, endothelial dysfunction, and hypercoagulability (11). The benefits and adverse effects of EBP in patients with COVID-19 have not been formally studied. Therefore, patients in whom EBP is being considered need to be selected carefully. If used, EBP therapies should be selected on the basis of the pathophysiology they are designed to target. Numerous clinical criteria (body temperature, hemodynamic status, need for vasopressor support, respiratory status and oxygenation, multiorgan failure score, cardiac and kidney function), as well as laboratory parameters (lymphocyte count, concentration of cytokines, ferritin, LDH, D-dimers, monocytic expression of HLA, myoglobin, troponin, CRP, endotoxin activity, procalcitonin and culture results) may be useful in evaluating the suitability of a patient for initiation of EBP (11, 13, 15). The precise indication for EBP in patients with COVID-19 remains to be determined. There are limited data regarding the timing of initiation or duration of using EBP, and further researches are needed.

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; EBP, extracorporeal blood purification; HCO, high cut-off; HP, hemoperfusion; LDH, lactate dehydrogenase; MCO, medium cut-off; MOF, multiorgan failure; PAMPs, pathogen-associated molecular patterns; RRT, renal replacement therapy; TPE, therapeutic plasma exchange.

OUTCOME

Although the reported incidence of AKI among hospitalized patients with COVID-19 varies widely, recent studies from the EU and USA have suggested an incidence of up to 40% (78, 88, 115). Evaluation and treatment of AKI in COVID-19 patients are similar to AKI in non-COVID-19 patients, with supportive measures being the cornerstone of management.AKI among hospitalized patients is associated with poor prognosis, increased length of stay, and increased health care costs. Patients who survive AKI appear to be at an increased risk of death and incident CKD or even end-stage renal disease (ESRD) (116, 117) (Figure 11).

Regardless of the need for dialysis or recovery of kidney function at discharge, hospitalized patients with COVID-19 who experience any form of AKI should probably be followed up closely after discharge to assess the ongoing kidney function.
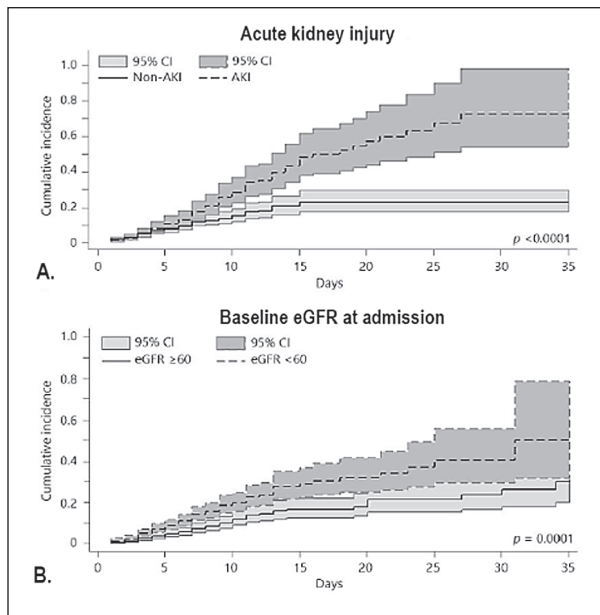
Fig. 11. *PAKI and in-hospital mortality*

Cumulative incidence of in-hospital mortality in COVID-19 patients by AKI:
  A. Admitting estimated glomerular filtration rate (eGFR);
  B. Shadows show the 95% confidence interval (117).

Zahid et al. investigated in-hospital mortality associated with AKI in COVID-19 patients (117). Overall, the in-hospital mortality was 40.1% in COVID-19 patients. A significantly higher in-hospital mortality was observed in patients with an eGFR <60 mL/min/1.73 m2 and elevated BUN at presentation. Furthermore, patients aged ≥75, those with preexisting comorbidities (diabetes mellitus, stroke and malignancy), arterial oxygen partial pressure/fractional inspired oxygen ratio <200 mm Hg, initial systolic blood pressure <100 mm Hg, elevated presenting BUN, eGFR <60 mL/min/1.73 m2 at presentation, and in-hospital AKI stage 2 and stage 3 were all associated with a higher in-hospital mortality. RRT did not improve survival (117)

R E F E R E N C E S

1. https://www.who.int/data#reports.

2. Arentz M, Yim E, Klaff L *et al*. Characteristics and outcomes of 21critically ill patients with COVID-19 in Washington State. JAMA 2020; 323: 1612-4.

3. Grasselli G, Zangrillo A, Zanella A *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy**.** JAMA 2020; 323: 1574-81.

4. Huang C, Wang Y, Li X *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

5. Wei-Jie G, Zheng N, Yu H *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382:1708-20.

6. Zhou F, Yu T, Du R *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-62.

7. Luwen W, Xun L, Hui C *et al*. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol 2020; 51: 343-8.

8. Papadimitriou JC, Drachenberg CB, Kleiner D *et al*. Tubular epithelial and peritubular capillary endothelial injury in COVID-19 AKI. Kidney Int Rep 2021; 6(2): 518-25. doi: https://doi.org/10.1016/j.ekir.2020.10.029.

9. Su H, Yang M, Wan C *et al*. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020; 98:219-27.

10. Yichun C, Ran L, Kun W *et al*. Kidney disease is associated within-hospital death of patients with COVID-19. Kidney Int 2020;97: 829-38.

11. Nadim MK, Forni LG, Mehta RL *et al*. COVID-19-associated acute kidney injury: consensus report of the 25[th]Acute Disease Quality Initiative (ADQI) Workgroup. Nature Rev Nephrol 2020; 16(12): 747-64.

12. Xizi Z, Youlu Z, Li Y. Acute kidney injury in COVID-19: the Chinese experience. SemNephrol 2020; 40(5): 430-42.

13. Fominskiy EV, Scandroglio AM, Monti G *et al*. Prevalence, characteristics, risk factors, and outcomes of invasively ventilated COVID-19 patients with acute kidney injury and renal replacement therapy. Blood Purif 2020; 13: 1-8.

14. Hong KS, Lee KH, Chung JH *et al*. Clinical features and outcomes of 98 patients hospitalized with SARS-CoV-2 infection in Daegu, South Korea: abrief descriptive study. Yonsei Med J 2020; 61: 431-7.

15. Uribarri A, Nez-Gil IJ, Aparisi A *et al*. Impact of renal function on admission in COVID-19 patients: an analysis of the international HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID 19) Registry. J Nephrol 2020; 33: 737-45.

16. Imam Z, Odish F, Gill I *et al*. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020; 288: 469-76.

17. Husain-Syed F, Wilhelm J, Kassoumeh S *et al*. Acute kidney injury and urinary biomarkers in hospitalized patients with coronavirus disease 2019. Nephrol Dial Transplant 2020; 35: 1271-4.

18. Li Z, Wu M, Yao J *et al*. Caution on kidney dysfunctions of COVID-19 patients. SSRN Electron J 2020; doi: 10.1101/2020.02.08.20021212

19. Gagliardi I, Patella G, Michael A *et al*. COVID-19 and the kidney: from epidemiology to clinical practice. J Clin Med 2020; 9: 2506.

20. Cheng Y, Luo R, Wang K *et al*. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020; 97: 829-38.

21. Corman VM, Lienau J, Witzenrath M. Coronaviruses as the cause of respiratory infections. Internist (Berl) 2019; 60: 1136-45.

22. Ji W, Wang W, Zhao X et al. Cross-species transmission of the newly identified coronavirus 2019-nCoV. J Med Virol 2020; 92: 433-40.

23. Lam TT-Y, Shum MH-H, Zhu HC et al. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. BioRxiv 2020; 583: 282-5.

24. Lu R, Zhao X, Li J et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-74.

25. Numbers SIN, Coronavirus disease 2019 (COVID-19). Sci Total Environ 2020; 2019: 200490.

26. Boroujeni EK, Kellner SJ, Pezeshgi A. COVID-19 and kidney; a mini-review on current concepts and new data. J Nephropharmacol 2020; 10: e01.

27. Morse JS, Lalonde T, Xu S, Liu, WR. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. Chembiochem 2020; 21: 730-8.

28. Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 cell entry depends on ACE-2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-80.

29. Guzzi PH, Mercatelli D, Ceraolo C, Giorgi FM. Master regulator analysis of the SARS-CoV-2/human interactome. J Clin Med 2020; 9: 982.

30. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun 2020; 526: 135-40.

31. Zou X, Chen K, Zou J et al. Single-cell RNA-seq data analysis on the receptorACE-2 expression reveals the potential risk of different human organs vulnerableto 2019-nCoV infection. Front Med 2020; 14: 185-92.

32. Mercante G, Ferreli F, De Virgilio A et al. Prevalence of taste and smell dysfunction in coronavirus disease 2019. JAMA Otolaryngol Head Neck Surg 2020; 146: 723-8.

33. 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.

34. Izzedine H, Jhaver KD. Acute kidney injury in patients with COVID-19: an update on the pathophysiology. Nephrol Dial Transplant 2021; 25;36(2):224-6.

35. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol 2020;31: 1683-7.

36. Diao B, Feng Z, Wang C, Wang H et al.Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [Preprint]. medRxiv: 2020.03.04.20031120. 10.1101/2020.03.04.20031120

37. Ng JH, Bijol V, Sparks MA et al. Pathophysiology and pathology of acute kidney injury in patients with COVID-19. Adv Chronic Kidney Dis 2020; 27(5): 365-76.

38. Ye M, Wysocki J, William J et al. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. J Am Soc Nephrol 2006; 17: 3067-75.

39. Ajaimy M, Melamed ML. COVID-19 in patients with kidney disease. CJASN 2020; 15: 1087-9.

40. Liu J, Li, S Liu J et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020; 55: 192763.

41. Fensterl V, Sen GC. Interferons and viral infections. Biofactors2009; 35: 14-20.

42. Lagunas-Rangel, FA, Chávez-Valencia V. High IL-6/IFN-ratio could be associated with severe disease in COVID-19 patients. J Med Virol2020; 92: 1789-90.

43. Couturier A, Ferlicot S, Chevalier K et al. Indirect effect of severe acute respiratory syndrome coronavirus 2 on the kidney in coronavirus disease patients. Clin Kidney J 2020; 13: 347-53.

44. Vučićević Ž. Interaktivni učinci akutne plućne ozljede, mehaničke ventilacije i akutnog oštećenja bubrega. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 616-36. (in Croatian)

45. Kes P, Jurić I, Bašić Jukić N. Rabdomioliza i akutno oštećenje bubrega. In: Kes P et al, editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 307-25. (in Croatian)

46. Planinc D, Kes P. Srčano-bubrežni sindrom tipa 1. In: Kes P et al., editors. Akutno oštećenje bubrega, Zagreb: Medicinska naklada, 2019; pp 559-86. (in Croatian).

47. Novosel D, Kes P. Sekundarni akutni srčano-bubrežni sindrom tipa 5. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 599-615. (in Croatian)

48. Bohn MK, Hall A, Sepiashvili et al. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. Physiology 2020; 35: 288-301.

49. Tang N, Li D, Wang X et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-7.

50. Mezalek ZT, Khibri H, Ammouri W et al. COVID-19 associated coagulopathy and thrombotic complications. Clin Appl Thromb Hemost 2020; 26: 1-10.

51. Martin-Rojas RM, Perez-Rus G, Delgado-Pinos VE et al. COVID-19 coagulopathy: an in-depth analysis of the coagulation system. Eur J Haematol 2020; 105: 741-50.

52. Ranucci M, Ballotta D, Dedda U et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020; 18: 1747-51.

53. Gao Y, Li T, Han M et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020; 92: 791-6.

54. Tanaka T, Narazaki M, Kishimoro T et al. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 2016; 8: 959-70.

55. Shi W, Lv J, Lin l. Coagulopathy in COVID-19: focus on vascular thrombotic events. J Mol Cell Cardiol 2020; 146: 32-40.

56. Bertram S, Heurich A, Lavander H et al. Influenza and SARS-coronavirus activating proteasesTMPRSS2 and HATare expressed at multiple sites in human respiratory and gastrointestinal tract. PLoA One 2012; 7: e35876.

57. Mizuiri S, Ohashi Y. ACE and ACE-2 in kidney disease. World J Nephrol 2015; 4: 74-82.

58. Fajnzylber J, Regan J, Coxen K.SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nature Commun 2020; 11: 5493.

59. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395: 1417-8.

60. Perico L, Benigni A, Casiraghi F et al. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nature Rev Nephrol 2020; 19: 46-64.

61. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. JAMA 2020; 323(5): 2195-8.

62. Ahmadian E, Khatibi SMH, Soofiani SR et al. COVID-19 and kidney injury: pathophysiology and molecular mechanism. Rec Med Virol 2020; e2176: 1-13.

63. Del Vecchio L, Locatelli F. Hypoxia response and lung and kidney injury: possible implications for therapy of COVID-19. CKJ 2020; 13(4): 494-9.

64. USCfDCaP (CDC). Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19 [Internet]. Atlanta: CDC; 2020 [cited 13 November 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extraprecautions/evidence-table.html.

65. Izzedine H, Jhaveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. Kidney Int 2020; 97: 1297-8.

66. Rački S, Jelić Pranjić I, Pavletić Peršić M. Kontrastna nefropatija. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp. 217-24. (in Croatian)

67. Husedžinović I, Šribar A. Akutno oštećenje bubrega u sepsi. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 225-37. (in Croatian)

68. Gattinoni L, Chiumello D, Caironi P et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Int Care Med 2020; 46: 1099-102.

69. Xia P, Wen Y, Duan Y et al. Clinicopathological features and outcomes of acute kidney injury in critically ill COVID-19 with prolonged disease course: a retrospective cohort. J Am Soc Nephrol 2020; 31(9): 2205-21.

70. Golmai P, Larsen CP, DeVita MV et al. Histopathologic and ultrastructural findings in postmortem kidney biopsy material in 12 patients with AKI and COVID-19. J Am Soc Nephrol 2020; 31(9): 1944-7.

71. Rapkiewicz AV, Mai X, Corsons SE et al. Megakariocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. E Clin Med 2020; 24: 100434.

72. Hanley B, Naresh KN, Roufosse C et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe 2020; 1(6): e245-e253.

73. Deshmukh V, Motwani R, Kumar A et al. Histopathological observations in COVID-19: a systematic review. J Clin Pathol 2020; 0: 1-8.

74. Kant S, Menez SP, Hanouneh M et al. The COVID-19 nephrology compendium: AKI, CKD, ESKD and transplantation. BMC Nephrol 2020; 21: 449.

75. Kissling S, Rotman S, Gerber C et al. Collapsing glomerulopathy in a COVID-19 patient. Kidney Int 2020; 98(1): 228-31.

76. Puelles VG, Lutgehetmann M, Lindenmeyer MT et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med 2020; 383: 590-2.

77. Miller SE, Goldsmith CS. Caution in identifying coronaviruses by electron microscopy. J Am Soc Nephrol 2020; 31: 2223-4.

78. Chan L, Chaudhary K, Saha A et al. AKI in hospitalized patients with COVID-19. JASN 2021; 32(1): 151-60.

79. Guan WJ, Ni ZY, Hu Y et al. Clinical charasteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-20.

80. Coronavirus Disease 2019 (COVID-19): Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html. (accessed on March 3, 2021)

81. Stokes EK, Zambrano LD, Anderson KN et al. Coronavirus disease 2019 case surveillance – United States, January 22-May 30, 2020. MMWR Early Release2020;69(24): 759-65.

82. Sarkesh A, Sorkhabi AD, Sheykhsaran E et al. Extrapulmonary clinical manifestations in COVID-19 patients. Am J Trop Med Hyg 2020; 103(5): 1783-96.

83. Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020; 323(18):1843-4.

84. Zhao J, Yuan Q, Wang H et al. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. Clin Infect Dis 2020; 71(16): 2027-34.

85. Wiersinga WJ, Rhodes A, Cheng AC et al. Pathophysiology, transmission, diagnosis and treatment of coronavirus disease 2019 (COVID-19). JAMA 2020; 324(8): 782-93.

86. Rodriguez-MoralesAJ, Cardona-OspinaJA, Gutiérrez-OcampoEet al. Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19).Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623.

87. KDIGO AKI Guideline. Kidney Int 2012; Suppl 1: 1-138.

88. Hirsch JS, Ng JH, Ross DW et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020; 98(1): 209-18.

89. Czawlytko C, Hossain R, White CS. COVID-19 diagnostic imaging recommendations. Appl Radiol 2020; 49(3): 10-5.

90. Aliondi R, Alghamdi S. Diagnostic value of imaging modalities for COVID-19. J Med Internet Res 2020; 22(8): e19673.

91. Kes P.Dijagnostički pristup bolesniku s akutnim oštećenjem bubrega. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp. 71-8. (in Croatian)

92. Vrkić N. Laboratorijska dijagnostika akutnog oštećenja bubrega. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp. 79-96. (in Croatian)

93. Kes P, Masin-Spasovska J. Analiza mokraće. In: Kes P et al., editors.Akutno oštećenje bubrega. Zagreb:Medicinska naklada, 2019; pp 97-107. (in Croatian)

94. Sjekavica I, BašićJukić N. Radiološkadijagnostikaakutnogoštećenjabubrega. In: Kes P et al., editors.Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 108-14. (in Croatian)

95. Ćorić M, BašićJukić N. Akutnooštećenjebubrega – indikacija za biopsijububrega.In: Kes P et al., editors.Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 115-20. (in Croatian)

96. Prkačin I. Prijebubrežno akutno oštećenje bubrega. In: Kes P et al., editors.Akutno oštećenje bubrega.Zagreb: Medicinska naklada, 2019; pp 121-32. (in Croatian)

97. Moore PK, Hsu RK, Liu KD. Management of Acute Kidney Injury: Core Curriculum 2018. Am J Kidney Dis 2018; 72(1): 136-48.

98. Brunetta Gavranić B. Važnost reguliranja glikemije u kritično bolesnihakutnim oštećenjem bubrega. In: Kes P et al., editors.Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 779-88. (in Croatian)

99. Kes P. Kontinuirano nadomještanje bubrežne funkcije. In: Kes P et al., editors.Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 959-98. (in Croatian)

100. Yang X-H, Sun R-H, Zhao M-J et al.Expert recommendations on blood purification treatment protocol for patients with severe COVID-19. Recommendation and consensus. Chron Dis Transpl Med 2020; 28; 6(2):106-14.

101. Ponkvar R. Liječenjeakutnogoštećenjabubreganekonvencionalnimmetodamapročišćavanjakrvi. In: Kes P et al., editors.Akutno oštećenje bubrega. Zasgreb: Medicinska naklada, 2019; pp 1040-7. (in Croatian)

102. Kes P. Hibridnaterapija u jediniciintenzivnogaliječenja. In: Kes P et al.,editors.Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 943-58. (in Croatian)

103. Di Mario F, Regolisti G, Di Maria A et al. Sustained low-efficiency dialysis with regional citrate anticoagulation in critically ill patients with COVID-19 associated AKI: a pilot study. K Crit Care 2021; 63: 22-5.

104. Hassanein M, Radhakrishnan Y, Vachharajani VT et al. COVID-19 and the kidney. Clev Clin J Med 2020; 87(10): 619-31.

105. Shaikh S, Umemoto GM, Vijayan A. Management of acute kidney injury in coronavirus disease 2019. Adv Chronic Kidney Dis 2020; 27(5): 377-82.

106. Rodriguez-Chagolla JM, Jimenez EV, Arellano LH et al. Peritoneal dialysis is an option for acute kidney injury management in patients with COVID-19. Blood Purif 2020; https://doi.org/10.1159/000511390

107. Altabas K, Klarić D, Vujčić B et al.Liječenjebolesnika s akutnimoštećenjembubregaperitonealnomdijalizom. In: Kes P et al., editors. Akutno oštećenje bubrega. Zagreb: Medicinska naklada, 2019; pp 1008-39. (in Croatian)

108. Suassuna RJH, de Lima QE, Rocha E et al. Technical note and clinical instructions for acute kidney injury (AKI) in patients with COVID-19: Brazilian Society of Nephrology and Brazilian Association of Intensive Care Medicine. Braz J Nephrol 2020; 42(Suppl 1): 22-31.

109. Naka T, Haase M, Bellomo R. 'Super high-flux' or 'high cut-off' hemofiltration and hemodialysis. Contrib Nephrol 2010; 166: 181-9.

110. Sanchez-Russo L, Billah M, Chancy J et al. COVID-19 and the kidney: a worrisome scenario of acute and chronic consequences. J Clin Med 2021; 10(900): 1-18.

111. Ronco C, Bagshaw SM, Bellomo R et al. Extracorporeal blood purification and organ support in the critically ill patient during COVID-19 pandemic: expert review and recommendation. Blood Purif2021; 50: 17-27.

112. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol 2020; 16(6): 308-10.

113. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020; 8: 738-42.

114. Ostermann M, Connor MJr, Kashani K. Continuous renal replacement therapy during extracorporeal membrane oxygenation: why, when and how? CurrOpin Crit Care 2018; 24(6): 493-513.

115. Hamilton P, Hanumapura P, Castelino L et al. Characteristics and outcomes of hospitalised patients with acute kidney injury and COVID-19. PLoS One 2020; 15(11): e0241544.

116. Ng JH, Hirsch JS, Hazzan A et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. Am J Kidney Dis 2021; 77(2): 204-15.

117. Zahid U, Ramachandran P, Spitalewitz S et al. Acute kidney injury in COVID-19 patients: an inner city hospital experience and policy implications. Am J Nephrol 2020; 51: 786-96.

S A Ž E T A K

AKUTNO OŠTEĆENJE BUBREGA U BOLESNIKA S COVID-19: IZAZOV ZA NEFROLOGE

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Akutno oštećenje bubrega (AOB) čest je nalaz u bolesnika s korona-virusnom bolešću 2019 (COVID-CoV-19), a povezano je s dugotrajnim bolničkim liječenjem, češćim prijmom bolesnika na odjel intenzivne skrbi i većom smrtnosti u usporedbi s bolesnicima s COVID-19 bez bolesti bubrega. Štoviše, stopa smrtnosti je izravno proporcionalna težini AOB-a. Patofiziologija AOB-a u bolesnika s COVID-19 posljedica je različitih specifičnih i nespecifičnih uzročnika. Mehanizmi specifični za COVID-19 su izravna stanična ozljeda zbog ulaska virusa u stanice putem ACE-2 receptora (koji su jako izraženi u bubrezima), neuravnoteženosti sustava renin-angiotenzin-aldosteron, teškim oštećenjem dišnog sustava i otpuštanja proupalnih citokina izazvanog teškom akutnom infekcijom koronavirusom 2 (SARS-CoV-2), koagulopatijom, mikroangiopatijom i kolapsnom glomerulopatijom. Nespecifični mehanizmi uključuju hemodinamske poremećaje, visoku razinu pozitivnog tlaka na kraju izdisaja u bolesnika kojima je potrebna mehanička ventilacija, sepsu, hipovolemiju, rabdomiolizu i primjenu nefrotoksičnih lijekova. Danas još ne znamo dovoljno o prevenciji i liječenju COVID-19. Terapijske mjere AOB-a u bolesnika s COVID-19 uključuju opće postupke i farmakološku terapiju COVID-19 s ciljem da se poprave poremećaji u hemodinamici i volumenu tjelesnih tekućina, nadomještanje bubrežne funkcije i uporabu uređaja za potporu drugim organskim sustavima. Dugoročna prognoza je zasad nepoznata. Međutim, može se s velikom vjerojatnosti pretpostaviti da će prognoza biti povezana s etiologijom AOB-a. Bolesnici s tromboembolijskim komplikacijama i kolapsnom glomerulopatijom mogu razviti teži stadij kronične bolesti bubrega u usporedbi s onima koji imaju drugu vrstu oštećenja bubrega (npr. akutni tubulointersticijski nefritis). Rezultati ranih istraživanja upućuju na to da će oko trećine bolesnika koji prežive AOB uzrokovan bolešću COVID-19 ostati ovisni o dijalizi.

Ključne riječi: sindrom akutnog respiratornog distresa, akutno oštećenje bubrega, receptor enzima konvertaze angiotenzina 2, COVID-19, sindrom otpuštanja citokina, izvantjelesna potpora organima, nadomještanje bubrežne funkcije, SARS-CoV-2