IN THE NAME OF GOD

A.Ahmadi
SHAHEED BEHESHTI UNIVERSITY

ACUTE KIDNEY INJURY

The Critically ill patienta with AKI
General consideration

- Approximately 20% of hospitalized patients and up to 60% of intensive care unit (ICU) patients experienced AKI.

- which significantly increases both short and long term morbidity and mortality rates
- There was a stepwise increase in mortality with increasing AKI severity [KDIGO]

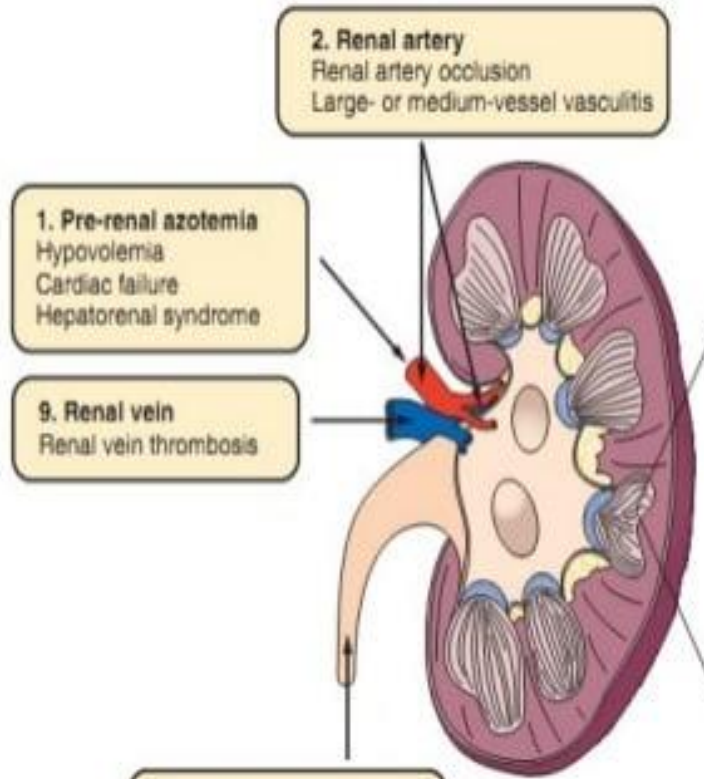
- Acute kidney injury (AKI):

  is the clinical term used for decline or loss of renal function.

- It is associated with chronic kidney disease (CKD)

Causes of AKI		
Pre-Renal	Intrinsic	Post-Renal
Pathology leading to decreased renal blood flow	Pathology causing direct renal parenchymal damage	Mechanical obstruction along the urinary tract
Hypovolemia	Acute tubular necrosis	Benign prostatic hypertrophy
Heart failure	Interstitial nephritis	Urethral stricture
Liver failure	Glomerulonephritis	Tumors with mass effect

Causes of AKI



1. Pre-renal azotemia
Hypovolemia
Cardiac failure
Hepatorenal syndrome

2. Renal artery
Renal artery occlusion
Large- or medium-vessel vasculitis

3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
Small-vessel vasculitis

4. Glomerular disease
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/Henoch-Schönlein purpura

5. Acute tubular necrosis
Ischemia
Nephrotoxins
Rhabdomyolysis
Radiocontrast agents

6. Acute interstitial nephritis
Drugs
Infection
Systemic disease

7. Intratubular obstruction
Cast nephropathy
Drugs
Crystalluria

8. Post-renal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis

9. Renal vein
Renal vein thrombosis

- Acute tubular injury (ATI): Prerenal, intrarenal, postrenal and even unilateral insults can cause ATI
- Dissociation between clinical symptoms and histopathological findings (ATI may be mild and/or even absent) :

  include prerenal AKI caused by volume depletion as in cardiogenic, allergic or hemorrhagic shock
- In practice, a semiquantitative histopathological scoring of ATI as {mild, moderate or severe (or focal versus diffuse)} is preferable instead of the term acute tubular necrosis (ATN)

- ATN is much less common compared with ATI and requires prolonged and sustained tubular injury that is usually absent in acute AKI (The exception is cortical necrosis)

- The clinical AKI in humans is a diverse process with multiple etiologies and varying pathophysiology such that single treatment options are unlikely to prove effective

- The creatinine may not reflect the severity of AKI in patients who produce less creatinine, such as those who are malnourished or elderly.

- Urine output criteria detect patients with AKI 11 h earlier than serum creatinine criteria

Staging of AKI(KDIGO)

Stage	Serum Creatinine	Urine output
1	1.5-1.9 times baseline within 1 wk or ≥ 0.3 mg/dl increase within 48 hrs	<0.5ml/kg/h for 6-12 hrs
2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥ 12 hrs
3	3.0 times baseline or increase in serum creat to ≥ 4.0 mg/dl or initiation of RRT or in patients < 18 yrs, decrease in eGFR to <35ml/min per 1.73 m^2)	<0.3ml/kg/h for ≥ 24 hrs or Anuria for ≥ 12 hrs

- # AKI biomarkers:
  - AKI biomarkers have predominantly been restricted to research use and have not yet permeated clinical practice.
  - One reason for this discrepancy is the use of creatinine as a flawed gold standard for biomarker qualification

Article | Open Access | Published: 07 December 2017

Risk, Predictors, and Outcomes of Acute Kidney Injury in Patients Admitted to Intensive Care Units in Egypt

Samar Abd ElHafeez, Giovanni Tripepi, Robert Quinn, Yasmine Naga, Sherif Abdelmonem, Mohamed AbdelHady, Ping Liu, Matthew James, Carmine Zoccali & Pietro Ravani

Scientific Reports **7**, Article number: 17163 (2017) | Cite this article

PMID: 31092273 PMCID: PMC6521368 DOI: 10.1186/s13054-019-2468-8

Download PDF

Sections | Figures | References

Abstract

Introduction

Results

Discussion

Methods and Materials

- The major signifcant predictors for the development of AKI in the ICU:
- sepsis; hypovolemia; CKD; chronic cardiovascular diseases; age>60 years; diabetes mellitus; hypertension
- Sepsis and hypovolemia were common etiologies
- Acute kidney injury was associated with increased length of hospital stay and a very high absolute mortality rate.

- A majority of the excess risk of mortality associated with AKI was attenuated by its fluid volume and metabolic complications, particularly in severe AKI.

- The RRT is associated with a better outcome in patients with AKI-related complications

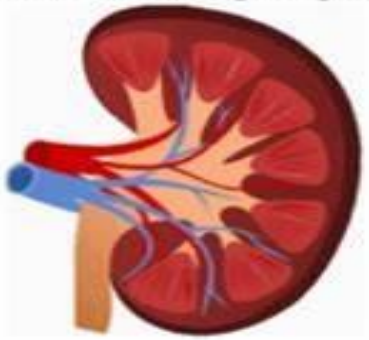
- Severe malnutrition among patients with AKI is an important risk factor for mortality
- Despite serum albumin level having limited value as a nutrition marker, its use as a predictor of mortality is well described in patients with AKI

- AKI pathophysiology:
  - Oxidative stress
  - Endothelial injury
  - Mitochondrial injury
  - Innate immunity

Ischemia Toxic injury

Sepsis

Acute kidney injury



Inflammation

Direct tubular injury through NK cells, neutrophils and macrophages

Cytokine/chemokine release

Vascular injury

Endothelial dysfunction

Microvascular obstruction

Vasoconstriction

Coagulopathy

Vascular leakage/edema

Tubular injury

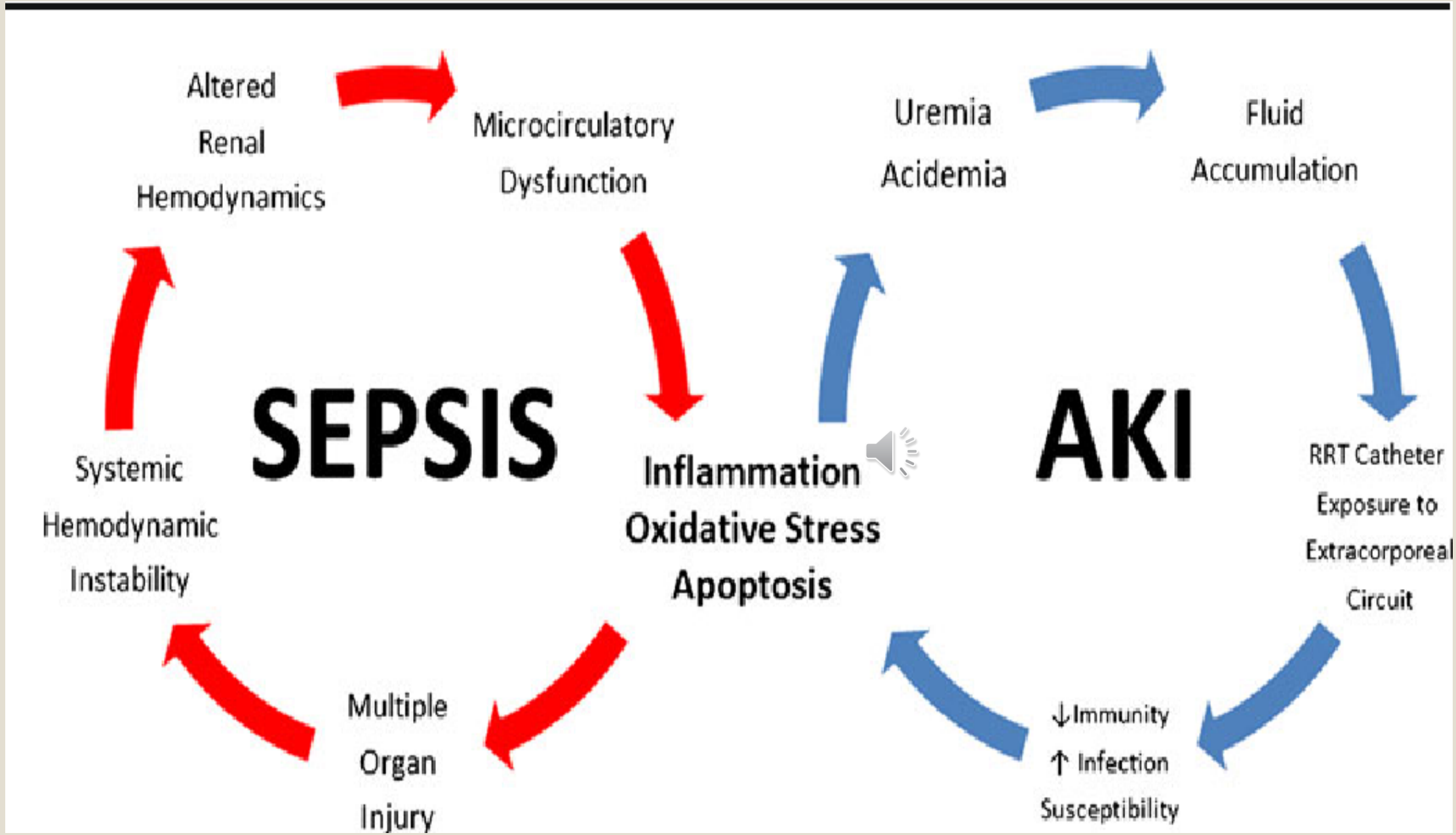
Cell death:
- necrosis
- apoptosis
- necroptosis

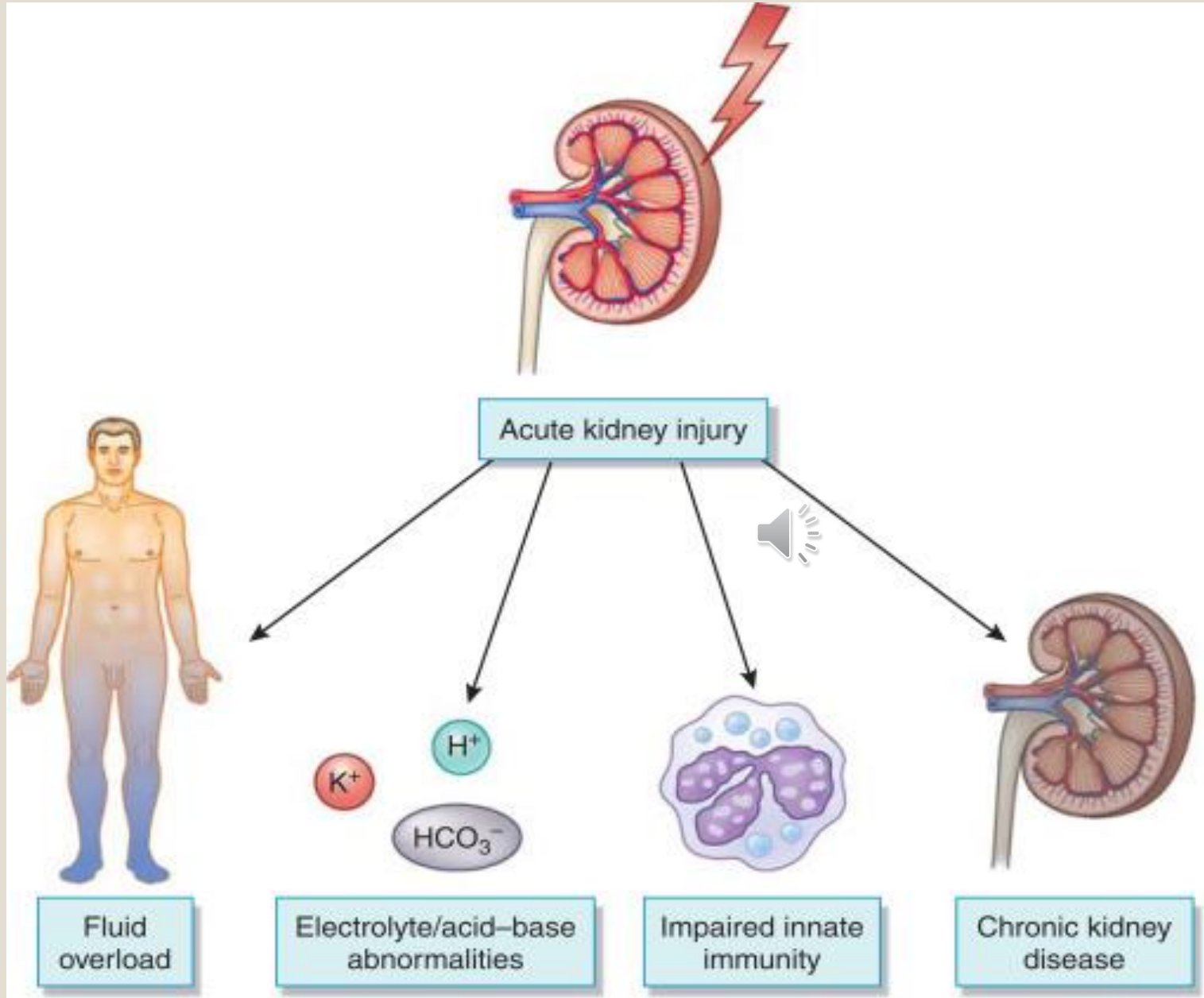
Brush border loss

Loss of cell polarity

Dedifferentiation

Tubular obstruction/casts


Altered
Renal
Hemodynamics
Microcirculatory
Dysfunction
Uremia
Acidemia
Fluid
Accumulation
SEPSIS
AKI
Systemic
Hemodynamic
Instability
Inflammation
Oxidative Stress
Apoptosis
RRT Catheter
Exposure to
Extracorporeal
Circuit
Multiple
Organ
Injury
↓Immunity
↑ Infection
Susceptibility


Acute kidney injury
Fluid overload
Electrolyte/acid–base abnormalities
Impaired innate immunity
Chronic kidney disease
H+
K+
HCO3−

COVID-19

- The COVID-19 has rapidly evolved into a global pandemic.
- about 5% develop severe symptoms, which can include acute respiratory distress syndrome, septic shock, and multiple organ failure
- Kidney involvement is frequent, with clinical presentation ranging from mild proteinuria to progressive AKI necessitating RRT
- As no specific treatment options exist for AKI secondary to COVID-19, intensive care is largely supportive

Pathophysiology of AKI in COVID-19

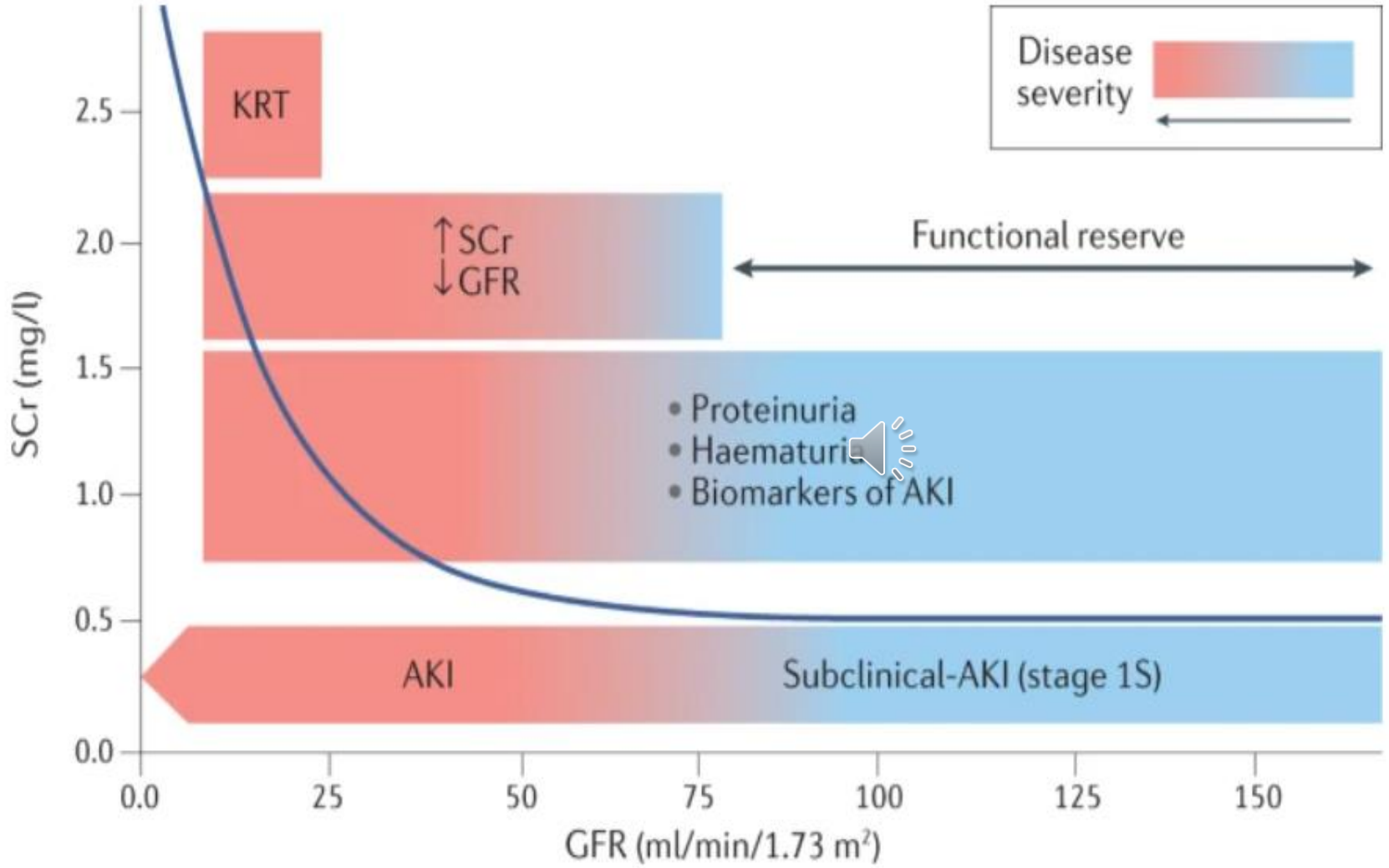
- multifactorial
- Predisposing factors (eg, sepsis, hypovolaemia, and nephrotoxins)
- Cardiorenal syndrome, particularly right ventricular failure secondary to COVID-19 pneumonia
- left ventricular dysfunction might lead to low cardiac output
- the endothelium is affected (lung and in the kidney)
- directly infect the renal tubular epithelium and podocytes through an ACE2-dependent pathway
- Immune response dysregulation (lymphopenia and cytokine storm)
- Rhabdomyolysis
- Macrophage activation syndrome
- Hypercoagulability
- endotheliitis

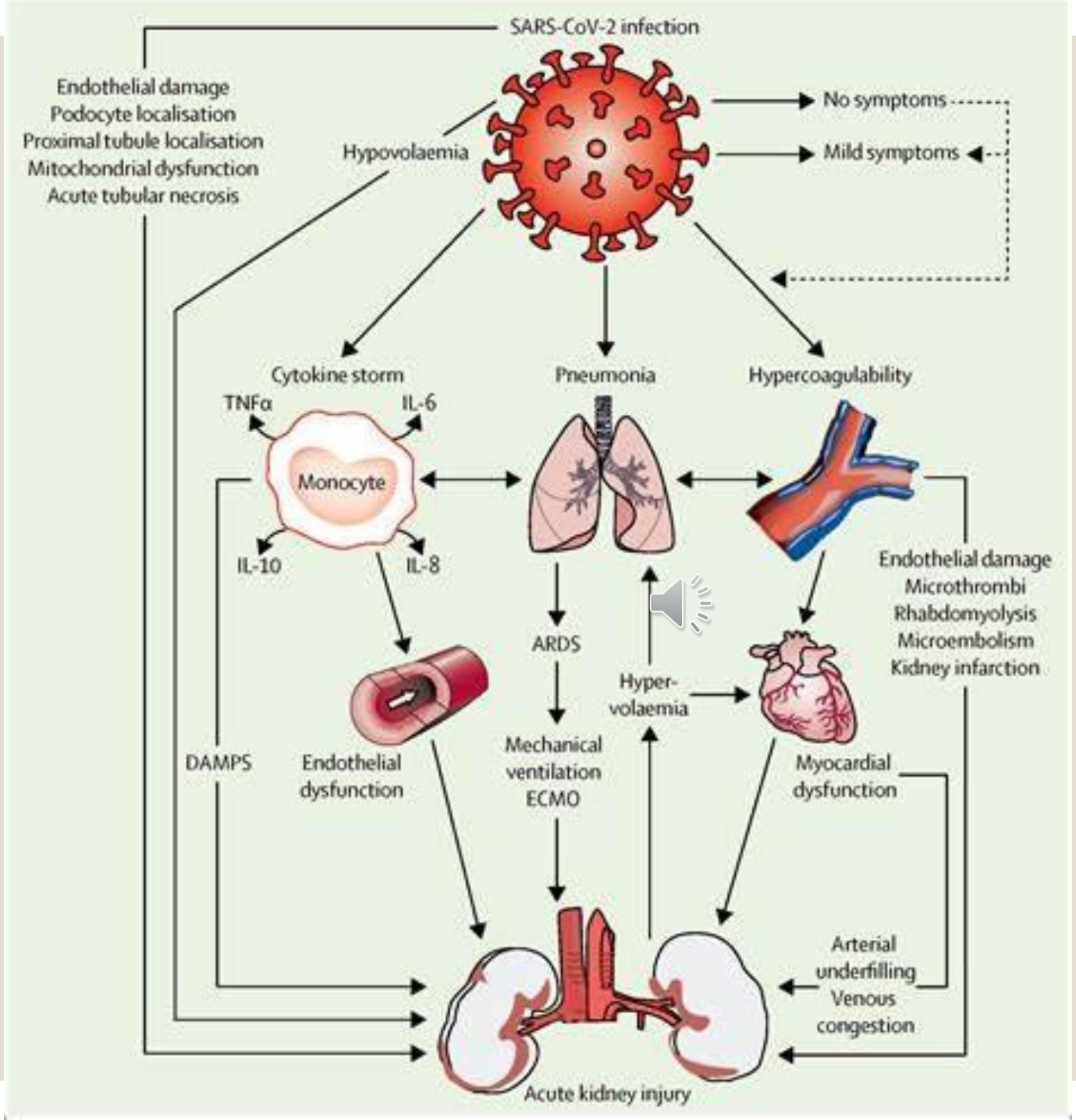
- Both early and late forms of AKI (that is, AKI at presentation and AKI developing after presentation) were associated with an increased risk of in-hospital mortality.

- Independent variables for AKI development were the presence of CKD, C-reactive protein level and requirement for ventilatory support.

- Clinical features:
- haematuria
- Proteinuria: low molecular weight rather than albuminuria, suggesting a tubular origin rather than glomerular injury, and can be used to identify patients with early-stage AKI
- Fanconi syndrome
- ↑Cr
- ↓urine out put

Fig. 2: Different stages of COVID-19-associated acute kidney injury.




SARS-CoV-2 infection
Endothelial damage
Podocyte localisation
Proximal tubule localisation
Mitochondrial dysfunction
Acute tubular necrosis
Hypovolaemia
No symptoms
Mild symptoms
Cytokine storm
Pneumonia
Hypercoagulability
TNFα
IL-6
Monocyte
IL-10
IL-8
Endothelial damage
Microthrombi
Rhabdomyolysis
Microembolism
Kidney infarction
ARDS
Hyper-
volaemia
DAMPS
Endothelial
dysfunction
Mechanical
ventilation
ECMO
Myocardial
dysfunction
Arterial
underfilling
Venous
congestion
Acute kidney injury

- Biopsy:
- The kidney injury seen in cases with the most severe respiratory disease in the ICU is predominantly tubular (66.7%)
- Collapsing glomerulopathy and focal segmental glomerulosclerosis were not seen in critically ill patients but were observed in 70.6% of cases not in the ICU
- Collapsing glomerulopathy correlated highly with the expression of high-risk APOL1 genotypes

- Histopathological findings:
- Acute tubular injury is common, it is often mild
- Systemic haemodynamic instability
- cytokine storm syndrome: levels of circulating cytokines are often lower in patients with COVID-19 than in patients with acute respiratory distress syndrome with causes other than COVID-19
- Tissue inflammation
- local immune cell infiltration
- Endothelial injury
- Microvascular thrombi
- viral invasion in the kidneys

Renal histology:

- Tubular injury: uncoupling between the extent of histological injury and decline of kidney function
- Collapsing glomerulopathy: COVID-19-associated nephropathy (COVAN), common mechanisms with HIV-associated nephropathy with podocyte injury
- Endothelial injury: increased levels of plasma biomarkers of endothelial injury (for example, soluble (s) E-selectin, sP-selectin, ANG2, sICAM1 and von Willebrand factor antigen) and platelet activation (soluble thrombomodulin) are associated with poor prognosis
- Thrombotic microangiopathy: biomarkers of coagulation and fibrinolysis activation (fibrinogen and D-dimer) have been repeatedly associated with an increased risk of death, sARS-CoV-2 has bind to platelets via ACE2, leading to platelet activation and immunothrombosis

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.
- Interferon

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.
- Interferon
- Complement

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.
- Interferon
- Complement
- Adaptive immunity

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.
- Interferon
- Complement
- Adaptive immunity
- Humoral immunity

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.
- Interferon
- Complement
- Adaptive immunity
- Humoral immunity
- cytokine storm syndrome

The immune and inflammatory response:

- Several alterations in both innate and adaptive immune responses
- Immunosenescence : inflammageing, a low-grade inflammatory state that may have a key role in determining organ dysfunction, as well as by ineffective T cell responses and antibody production…
- Inflammation: The enhanced release of inflammatory mediators by immune and resident kidney cells is likely to be a key mechanism of tissue damage in patients with COVID-19.
- Interferon
- Complement
- Adaptive immunity
- Humoral immunity
- cytokine storm syndrome
- ACE2 and the renin–angiotensin system

- # Non-specific factors:
- In addition to virus-specific responses, the pathogenesis of AKI in the context of COVID-19 most likely also involves factors that are not specific to the virus but are part of a general response to critical illness or its treatment:
- haemodynamic factors
- drug toxicity
- impact of organ support systems

- Another series from France demonstrated tubular injury in the most severely ill cohort whereas glomerular pathology was restricted to the non-ICU patients

Box 1 Factors that may contribute to COVID-19-associated acute kidney injury

Acute tubular injury

- Regional inflammation
- Direct viral infection
- Renal compartment syndrome
- Tissue hypoxia hypoperfusion leading to hypoxaemia, hypotension, hypovolaemia and heart failure
- Nephrotoxic-induced injury (potentially associated with the use of antibiotics (vancomycin, aminoglycosides, colistin) or antivirals (remdesivir, ritonavir))
- Rhabdomyolysis

Vascular injury

- Endotheliitis
- Microthrombi
- Thrombotic microangiopathy

Glomerular injury

- Collapsing glomerulopathy (potentially caused by interferon-associated podocyte injury)
- Glomerulonephritis

Interstitial injury

- Acute interstitial nephritis; infiltration by immune cells
- Interstitial oedema

- The major difference between COVID-19 AKI and other types of sepsis:
- the inconsistent finding of virus particles in epithelial cells combined with more prominent vascular alterations in COVID-19 AKI.

Vascular consequences of SARS-CoV-2 induced coagulopathy

SARS-CoV-2

Capillary obstruction by red blood cells

Coagulation activation

Fibrinoid necrosis, Glomerular ischemia

Kidney invasion via SARS-CoV-2 entry in proximal tubular cells and podocytes

Proximal convoluted tubule

Acute proximal tubular injury

Glomerule

Podocyte

Podocyte dysfunction

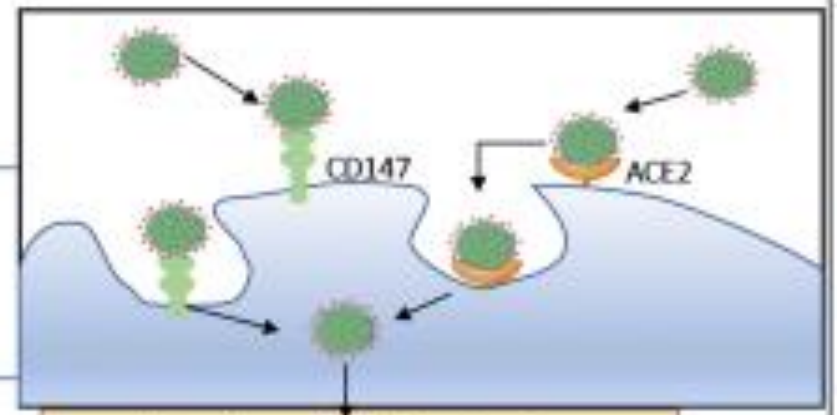
Mesangium

FSGS

Glomerular capillary

Arterioles

Distal convoluted tubule



Imbalanced RAAS activation
Glomerular dysfunction, Inflammation, fibrosis, vasoconstriction

IL1-β

TNFα

MCP

IL6

Cytokines elevation

Lung/heart dysfunction

High level of PEEP

Nephrotoxic drugs

Fluid restriction

Haemodynamic instability

ICU

Unspecific kidney injury factors

- No specific treatment for AKI is established except for certain glomerular or vascular diseases
- firstly, treatment for underlying disease
- secondly, maintenance of renal blood flow and perfusion to preserve kidney function and recovery
- third, supportive treatment for electrolyte disorders and uremic syndrome
- fourth, renal replacement therapy when needed

Intravenous Fluid Resuscitation

- Although administration of intravenous fluids in patients with sepsis and/or hypovolemia is beneficial initially, fluid overload, especially in later disease, may confer harm
- Intravenous fluids should be used judiciously in patients with AKI who are not "volume responsive.
- After significant volume resuscitation, even if patients remain volume responsive, vasopressor support should be considered to avoid markedly positive fluid balance.

- The choice of solution is controversial
- There is a clear indication for albumin in the setting of large-volume paracentesis for patients with end-stage liver disease because albumin infusion is associated with lower risk for AKI.
- Albumin (and likely other colloids) should be avoided in patients with traumatic brain injury due to an increased risk for death.
- there are no data to support the routine use of colloid for volume resuscitation.

- Administration of 0.9% saline solution is associated with increased extravascular volume and decreased renal cortical tissue perfusion compared to a balanced salt solution.
- Patients receiving normal saline solution are at risk for hyperchloremic metabolic acidosis

Diuretics

- In addition to preventing volume overload, loop diuretics theoretically attenuate ischemic tubular injury

- the use of diuretics in the setting of volume overload

Nutrition and Glucose Control

- AKI is a catabolic state, and patients with AKI may need enteral or parenteral nutritional support
- The enteral route is preferred due to the lower risk for infection (and lower volumes needed to administer equivalent calories).
- The intensive glycemic control was associated with higher mortality and a greater incidence of severe hypoglycemia

Blood Pressure Management

- 2 blood pressure goals: MAP goal (65-70 mm Hg)

  higher goal (80-85 mm Hg)
- There was no difference in mortality between the 2 treatment groups.
- However, patients with chronic hypertension in the higher MAP group had significantly lower rates of AKI and RRT
- Patients in the higher MAP group had higher rates of atrial fibrillation.

Clinical management of covid-19

- avoidance of nephrotoxins
- regular monitoring of serum creatinine and urine output
- haemodynamic monitoring
- Mitigation of volutrauma and barotrauma
- hypovolaemia should be corrected
- avoid volume overload

RRT and extracorporeal support

- If conservative management fails, RRT should be considered in patients with volume overload, especially those with refractory hypoxaemia
- CRRT is the preferred modality in haemodynamically unstable patients with COVID-19
- When RRT is carried out in conjunction with ECMO, RRT should be performed through venous access independent of the ECMO circuit to minimise clot formation in the latter

- in some patients because of the paucity of sites available for direct cannulation, the RRT outflow should be connected to the pre-oxygenator limb of the ECMO circuit, as the oxygenator can serve as a protective barrier and minimise risk of systemic gas embolism in the lungs
- The anticoagulation protocols for the extracorporeal circuit must be tailored to the needs of individual patients
- In CRRT, regional citrate anticoagulation is more efficacious than other anticoagulation methods

- in the early phases of cytokine storm, the application of haemoperfusion with sorbent cartridges might prevent cytokine induced kidney damage
- Extracorporeal treatments do not compromise the experimental antibody-based therapies used in COVID-19, such as tocilizumab, intravenous immunoglobulins, and convalescent plasma administration
- The upper size of molecules that can be removed with RRT or haemadsorption (around 60 kDa)
- The use of high cutoff or medium cutoff membranes in CVVHD to increase cytokine removal

- Lung-protective ventilation with tidal volume at 6 mL/kg predicted body weight might lead to hypercapnia, respiratory acidosis, increased need for vasopressors, and AKI
- In some patients, bacterial infection co-occurs with SARS-CoV-2 infection and a sepsis-like syndrome can develop

- RRT was associated with a better outcome only in the subgroups with AKI-related complication