MANAGEMENT OF COVID-19 PATIENTS

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ABSTRACT

The largest threat to the healthcare of mankind since the 1918 influenza pandemic was the outbreak of Coronavirus Disease 2019 (COVID-19). The first cases of COVID-19 were discovered in Wuhan in Hubei province, China, and COVID-19 was declared a pandemic on 11 March 2020. According to WHO, as of 19 June 2022, over 536 million confirmed cases and over 6.3 million deaths have been reported globally. COVID-19 presents with symptoms affecting the respiratory, gastrointestinal, and neurologic systems. The patients at risk of severe symptoms include the elderly, people with comorbidities, the immunocompromised, and the unvaccinated. Treatment of patients with COVID-19 depends on the severity of the disease, the patient's health condition, and the resources available. In this review, we discussed extensively the strategies utilized and recent advancements in the respiratory, cardiovascular, and renal management of COVID-19 patients. Close contact with infected individuals who produce respiratory droplets is the most common mechanism of person-to-person transmission of SARS-CoV-2 infection. As such, safety measures to be followed by healthcare personnel are also discussed.

Keywords: COVID-19, SARS-COV-2, clinical management

INTRODUCTION

The largest threat to the healthcare of mankind since the 1918 influenza pandemic was the outbreak of Coronavirus Disease 2019 (COVID-19)[1]. The first cases of COVID-19 were discovered in Wuhan in Hubei province, China and since then, it has spread all over the world, infecting millions of people and killing several in the process[1,2]. According to WHO, as of 19 June 2022, over 536 million confirmed cases and over 6.3 million deaths have been reported globally[3]. In a bid to reduce the spread of the infection, multiple strategies have been adopted, which include social distancing, drug trials, and the recent production of vaccines[4,5].

Coronaviruses (CoVs) are a class of genetic viruses found in a wide range of host species, including birds and mammals. The novel Coronavirus was shown to be closely related structurally to the virus that causes Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)[1]. Human susceptible coronavirus (HCoV) causes mild respiratory symptoms similar to a common cold. Other coronaviruses like SARS and MERS lead to severe respiratory tract infections. (6) COVID-19 is spread by droplets, respiratory secretions, and contact with infected people[2,7].

EPIDEMIOLOGY

In December 2019, the first patients of COVID-19 were reported to have visited a wet seafood market in Wuhan, China. Molecular analysis of their blood revealed that the pathogen was a new coronavirus[8]. COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020[9].

The first confirmed case of COVID-19 infection in Africa was imported from Europe into Egypt on the 14th of February, 2020, and eventually spread across countries on the continent[10]. In Nigeria, the first confirmed case of COVID-19 was identified on the 27th of February, 2020 in a visiting Italian with the number of cases steadily rising over time[11].

RISK FACTORS

Risk factors for contracting COVID-19 range from demographic factors like age, sex, and ethnicity to other factors like underlying comorbidities, diet, and lifestyle habits[7,12].

The mortality rate of COVID-19 is seen to be more in individuals >60years of age [2]. Blacks and other minority races have also been shown to be disproportionally affected by the virus and have a higher risk of hospitalization and mortality[12]. There is evidence of an increased risk of

COVID-19 in people with an underlying disease[2]. The most severe cases of COVID-19 were found among individuals who were living with hypertension, respiratory and cardiovascular disease, diabetes, and cancer[5]. Other studies have shown that smoking was associated with a higher risk of COVID-19. Asides from this, smokers are likely to have more severe respiratory complications and require hospitalization[2]. Males have been shown to have an increased risk of COVID-19. This is attributed to their higher smoking rates and the presence of comorbidity[5].

PATHOPHYSIOLOGY AND CLINICAL FEATURES

Spike proteins on the membrane of SARS-COV-2 bind to its receptor on mammalian cells; Angiotensin Converting Enzyme 2 (ACE2). ACE2 in the lungs is the main target of SARS-COV-2. As the virus enters the host cell, it utilizes the cell machinery to replicate and infect surrounding cells. This leads to the destruction of type 2 Pneumocytes. The resulting consequences include:

1. Inflammation, which leads to reduced gas exchange and breathlessness

2. Increased vascular permeability, which leads to the development of pulmonary edema, which further reduces gas exchange

All of these result in a variety of symptoms including Acute Respiratory Distress Syndrome (ARDS)[13].

Symptoms of COVID-19 range from asymptomatic to mild or moderate to severe. Individuals with mild or moderate infections usually experience flu-like symptoms. In more serious cases, patients develop multiple organ failures and eventually die. The patients at risk of severe symptoms include the elderly, people with comorbidities, the immunocompromised, and the unvaccinated[7].

COVID-19 presents with symptoms affecting the respiratory, gastrointestinal, and neurologic systems. A study conducted on the clinical features of patients with 2019 novel coronavirus in Wuhan, China showed that the most common symptoms of the onset of COVID-19 include fever (98%), cough (76%), and fatigue (44%). Other less common symptoms include sputum production (28%), headache (8%), and diarrhea (3%)[14]. In a cohort study in Italy, 53% of participants were found to have taste and olfactory disorders. Infected individuals from the US and China also presented with neurological disturbances such as altered mental state and stroke and cardiovascular symptoms including cardiac arrhythmia and heart failure[15]. A risk stratification was developed in a retrospective study in Wuhan Huoshenshan Hospital to help clinicians make decisions easily and optimize the use of limited medical resources. It enables the early prediction of disease progression in asymptomatic, severe presymptomatic, and non-severe presymptomatic patients based on 5-10 laboratory indicators[16]. In another study, patients whose conditions are regarded to be severe and/or are on respiratory support are classified into the high-risk group, and others were put under the low/mild risk group[17].

TREATMENT STRATEGY

Treatment of patients with COVID-19 depends on the severity of the disease, the patient's health condition, and the resources available[2]. Treatment employed ranges from mild strategies including rest and fluid intake to more severe ones like drugs and respiratory support.

Drugs that are approved for use include;

1. Antiretroviral drugs eg Remdesivir.

Remdesivir is an RNA-dependent polymerase inhibitor. It was originally developed for the treatment of the Ebola Virus[18]. Its use in COVID-19 antiviral therapy has shown significant benefits with patients having a shorter recovery time and were at a lesser risk of the disease progressing to a more severe condition[19].

2. Immunomodulators eg Glucocorticoids, Convalescent plasma, Dexamethasone, IL-6 blockers, and Baricats.

Glucocorticoids. In a randomized trial of COVID-19 patients, Dexamethasone reduced deaths in ventilated patients and patients receiving supplemental oxygen, but not in patients who did not require oxygen[18].

Convalescent plasma. This is gotten from the blood of individuals that have been cured of COVID-19. It is considered to be safe and beneficial as it provides an alternate and accessible source of antiviral antibodies [18]. Convalescent plasma and immunoglobulin G treatment are given to some severe COVID-19 cases. [7]

Other drugs that have been tried for COVID-19 treatment include; Hydroxychloroquine. This is an immunomodulatory drug that has been used for decades to treat malaria and autoimmune diseases such as systemic lupus erythematosus and inflammatory arthritis[20].

Another drug that has shown positive results is paxlovid. It has significantly reduced hospital admissions and mortality rates in patients with COVID-19[21,22].

PULMONARY MANAGEMENT

Common features of COVID-19 infection include difficulty in breathing and pulmonary symptoms[2]. These symptoms are managed effectively from the supply of oxygen to the implementation of pulmonary rehabilitation in mild and severe cases respectively. The management chosen depends on the severity of the patient[23]. WHO recommends supplemental oxygen therapy for patients with respiratory distress, hypoxemia, or shock with a target of SPO2 greater than 94%[2].

The clinician's first response is to increase oxygenation by oxygen administration and noninvasive respiratory

support eg high flow nasal O2, CPAP and BiPAP. Oxygen therapy is sufficient in mild cases of Covid to alleviate the symptoms. It can be used for patients in respiratory distress by the use of facemask oxygen or reservoir bags[24].

If the above does not improve oxygenation, invasive mechanical support will be needed via intubation and mechanical ventilation[25]. Extracorporeal Membrane Oxygenation (ECMO) is particularly used to decrease the risk incurred from mechanical ventilation and supports patients with failing lungs. The use of ECMO was originally thought to have high mortality in patients with COVID. The number of deaths is now shown to be no less different from other respiratory distresses[26].

The evidence for pulmonary rehabilitation for patients that present with respiratory symptoms eg long covid provides strong support for the development of pulmonary rehabilitation programs for patients with COVID-19. A small study in China on 9 discharged patients with SARS who underwent pulmonary rehabilitation for 3 weeks showed a significant difference in the perfusion rate for the pulmonary function of the patients different from the baseline value [27].

CARDIOVASCULAR MANAGEMENT

Presence of pre-existing cardiovascular (CV) disease and/or development of CV complications like Acute Cardiac Injury (ACI), Shock, and Arrythmia are associated with significantly worse outcome in COVID-19 patients [28]. Common mechanisms responsible for CV complications include direct myocardial activity, systemic inflammation, altered myocardial demand-supply ratio, plaque rupture and coronary thrombosis, adverse effects of various therapies, and electrolyte imbalances [28].

With an incidence between 8-12%, ACI is the most commonly described complication evidenced by increased troponins or abnormal ECG findings [2,29]. ACI is seen in up to one-fifth of hospitalized patients, usually late in the disease's onset and is associated with a poor prognosis (2). It has been suggested that via direct viral myocardial activity is the most common mechanism, but autopsy studies have not found such evidence [2,30].

Similarly, both tachy- and brady-arrhythmias are known to occur in COVID-19. According to a study that described clinical profile and outcomes in 138 Chinese patients, arrhythmia incidence was reported 16.7%, even much higher (44.4%) in those in ICU as compared to those that are not in ICU (8.9%) [31]

A considerable number of critically-ill SARS-CoV-2 patients experience shock during their hospital stay. Cardiogenic shock, secondary infections, sepsis as well as cytokine storm are all common causes of this [2]. Cytokine blockade therapies such as IL-6 blockers can be effective in patients with cytokine storm. Also, early intervention in patients with secondary infections that may progress to septic shock, followed by initial resuscitation with crystalloids and then continuing with vasopressors supplied through a central line, has been suggested to be helpful [2].

Despite claims that these agents upregulate ACE2 receptors and SARS-CoV-2 binds to ACE2 to gain entry into human cells, many leading professional societies have strongly advised against discontinuing clinically-indicated ACEi/ARB therapy in the event the patient develops COVID-19, against claims that. This is because there is currently no experimental or clinical data to back up these claims[29].

RENAL MANAGEMENT

Kidney involvement is frequent, with clinical presentation ranging from mild proteinuria to progressive acute kidney injury (AKI) necessitating renal replacement therapy (RRT) [32]Acute kidney injury (AKI) has been reported in up to 25% of critically-ill COVID-19 patients in the ICU, especially in those with underlying comorbidities (33) It is considered a marker of disease severity and a negative prognostic factor for survival [32].

The pathophysiology of COVID-19-induced AKI could be linked to both unspecific and COVID-specific mechanisms, like direct viral-mediated mechanism via the highly expressed receptor (ACE2) in the kidney, an imbalanced renin–angiotensin–aldosterone system, pro-inflammatory cytokines elicited by the viral infection, and thrombotic events [33] Hemodynamic changes, right heart failure, high PEEP in patients requiring mechanical ventilation, hypovolemia, nephrotoxic drug administration, and nosocomial sepsis are all non-specific causes [33].

To date, there is no specific treatment for COVID-19 induced AKI (d). This form of care strategy remains largely supportive [32] Early recognition of kidney involvement in COVID-19 and use of preventive and therapeutic measures to limit subsequent AKI or progression to more severe stages are crucial to reduce morbidity and mortality [32]

Many studies have suggested the use of Kidney Disease Improving Global Outcomes (KDIGO) supportive guideline like the avoidance of nephrotoxins, regular monitoring of serum creatinine and urine output, and consideration of hemodynamic monitoring. However, none of them have reported AKI stages [32,33,34] Consequently, requires validation [34]

Another important option is to adjust fluid balance according to volume responsiveness and tolerance assessment. Volume depletion at admission might be common in patients with COVID-19 and the hypovolemia should be corrected to prevent AKI [32]. However, volume overload should be prevented.

If conservative management fails, RRT should be considered in patients with volume overload, especially those with refractory hypoxemia. Renal replacement therapy has been used in nearly 20% of the critically affected patients admitted in the ICU at a median of 15 days from illness onset [35]. Early initiation of RRT and sequential extracorporeal organ support (ECOS)[36] seem to provide adequate organ support and prevent progression of disease severity (figure 1). Continuous RRT (CRRT) is the preferred modality in hemodynamically unstable patients with COVID-19[29].

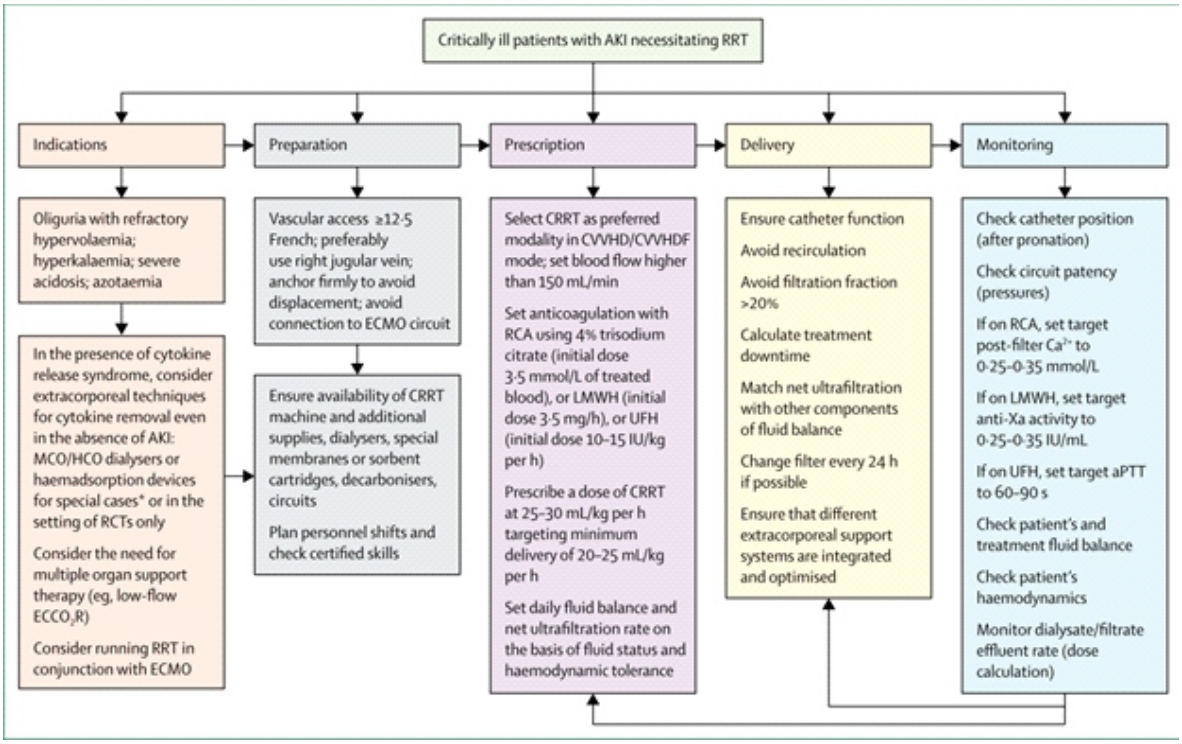

Figure 1: Management of acute kidney injury necessitating renal replacement therapy in patients with COVID-19

Management recommendations focus on AKI in COVID-19 rather than usual practice for AKI, and are based largely on our clinical experience. All therapeutic options need to be tested in rigorous studies and ideally randomized trials in the context of COVID-19. In the absence of specific therapies, all options should be considered according to each patient's needs. The extracorporeal therapies included in the figure for consideration can be complementary to pharmacological support. The activity targets for anticoagulant therapy are indicative only and should be tailored to each patient's characteristics and clinical condition. The general principle is that maximal anticoagulation should be achieved in the extracorporeal circuit with minimal systemic effects; if systemic anticoagulation is indicated, an integrated prescription should be considered.

PUBLIC HEALTH APPROACH (INFECTION CONTROL)

Close contact with infected individuals who produce respiratory droplets is the most common mechanism of person-to-person transmission of SARS-CoV-2 infection. Because the virus can remain active on inanimate surfaces for several hours, fomite transmission is a possibility[37]. Although airborne transmission is a possibility, it does not appear to be a significant mechanism. Due to a lack of personal protective equipment in varied contexts, this has particular ramifications. Smaller particles produced by aerosol-generating methods may linger in the air for longer. It appears doubtful that such particles will move far enough to cause secondary illness[38].

Isolation can be very effective. Outbreak can be contained if a series of timely measures are taken. These measures are implemented to contain and prevent the transmission of an infectious disease. Table VI shows safety measures to be followed by healthcare personnel in terms of infection control.

CONCLUSION

COVID-19 remains a large threat to mankind. The patients at risk of severe symptoms include the elderly, people with comorbidities, the immunocompromised, and the unvaccinated. Treatment of patients with COVID-19

Table VI. Precautionary measures for infection control among healthcare workers

Procedures	Precautionary measures
Examining or providing care for patients	Surgical mask, goggles or face shield, gown/apron and gloves
Performing AGPs* on patients	N95 respiratory masks, goggles or face shield, gown and gloves

*Aerosol generating procedures (AGPs) include endotracheal intubation, non-invasive ventilation such as BiPAP, manual ventilation before intubation with ambu bag, administration of nebulized medications, disconnecting a ventilator, positioning prone of a ventilated patient, tracheostomy, bronchoscopy, open suctioning of intubated patients and cardiopulmonary resuscitation. BiPAP, bilevel positive airway pressure

Source: Ref. 63

depends on the severity of the disease, the patient's health condition, and the resources available. There are different strategies and recent advancements in the respiratory, cardiovascular, and renal management of COVID-19 patients. Close contact with infected individuals who produce respiratory droplets is the most common mechanism of person-to-person transmission of SARS-CoV-2 infection.

REFERENCES

1. Fauci AS, Clifford Lane H, Redfield RR. Covid-19-Navigating the Uncharted. 2020;
2. Varghese G, John R, Manesh A, Karthik R, Abraham O. Clinical management of COVID-19. Indian Journal of Medical Research [Internet]. 2020;151(5):401. Available from: https://journals.lww.com/ijmr/Fulltext/2020/51050/Clinical_management_of_COVID_19.4.aspx
3. Weekly epidemiological update on COVID-19 - 22 June 2022 [Internet]. [cited 2022 Jun 23]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---22-june-2022
4. Dong Y, Dong Y, Mo X, Hu Y, Qi X, Jiang F, et al. Epidemiology of COVID-19 among children in China. Vol. 145, Pediatrics. American Academy of Pediatrics; 2020.
5. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. Available from: www.gov.uk/government/publications/covid-19-guidance-on-social-distancing-and-for-
6. Yin Y, Wunderink RG. INVITED REVIEW SERIES: RESPIRATORY INFECTIONS IN THE ASIA-PACIFIC REGION MERS, SARS and other coronaviruses as causes of pneumonia. 2017;
7. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak- A n update on the status. Vol. 7, Military Medical Research. BioMed Central Ltd.; 2020.
8. Sun J, He WT, Wang L, Lai A, Ji X, Zhai X, et al. COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. Vol. 26, Trends in Molecular Medicine. Elsevier Ltd; 2020. p. 483–95.
9. Budd J, Miller BS, Manning EM, Lampos V, Zhuang M, Edelstein M, et al. Digital technologies in the public-health response to COVID-19. Nature Medicine [Internet]. Available from: https://doi.org/10.1038/s41591-020-1011-4
10. Lone SA, Ahmad A. COVID-19 pandemic-an African perspective. 2020; Available from: https://doi.org/10.1080/22221751.2020.1775132
11. Daniel O, Bamidele J. Epidemiology of Coronavirus Disease (COVID-19) in Nigeria. Annals of Health Research. 2020 May 17;6(2):125–32.
12. Gao Y dong, Ding M, Dong X, Zhang J jin, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review COVID-19, critical illness, risk factors, SARS-CoV-2, severity. 2020;
13. Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression. 2020 [cited 2022 Jun 27]; Available from: www.physiologyonline.org
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020 Feb 15;395(10223):497–506.
15. Vetter P, Vu DL, L'Huillier AG, Schibler M, Kaiser L, Jacquerioz F. Clinical features of covid-19. Vol. 369, The BMJ. BMJ Publishing Group; 2020.
16. Shi L, Ding R, Zhang T, Wu W, Wang Z, Jia X,

et al. Comparative Characterization and Risk Stratification of Asymptomatic and Presymptomatic Patients With COVID-19. Frontiers in Immunology. 2021 Jul 9;12.
17. Alle S, Kanakan AI, Siddiqui S, Garg A, Karthikeyan A, Mehta P, et al. COVID-19 Risk Stratification and Mortality Prediction in Hospitalized Indian Patients: Harnessing clinical data for public health benefits. 2022; Available from: https://doi.org/10.1371/journal.pone.0264785
18. Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, Fotiou D, Migkou M, Tzanninis IG, et al. Emerging treatment strategies for COVID-19 infection. Vol. 21, Clinical and Experimental Medicine. Springer Science and Business Media Deutschland GmbH; 2021. p. 167–79.
19. (No Title). 2020;
20. Hydroxychloroquine: An old drug with new relevance. Available from: www.ccjm.org
21. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. Available from: http://dx.doi.org/10.1136/bmj.n2713
22. Wen W, Chen C, Tang J, Wang C, Zhou M, Cheng Y, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for COVID-19 : a meta-analysis. 2022; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=iann20
23. Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. Journal of Physiotherapy. 2020 Apr 1;66(2):73–82.
24. WHO-2019-nCoV-clinical-2020.4-chi.
25. Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, et al. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. Anesthesiology. 2020;1317–32.
26. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. The Lancet. 2021 Oct 2;398(10307):1230–8.
27. Yang LL, Yang T. Pulmonary rehabilitation for patients with coronavirus disease 2019 (COVID-19). Vol. 6, Chronic Diseases and Translational Medicine. KeAi Communications Co.; 2020. p. 79–86.
28. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Vol. 106, Heart. 2020.
29. Bansal M. Cardiovascular disease and COVID-19. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. 2020;14(3).
30. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. European Journal of Clinical Investigation. 2009;39(7).
31. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - Journal of the American Medical Association. 2020;323(11).
32. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Vol. 8, The Lancet Respiratory Medicine. Lancet Publishing Group; 2020. p. 738–42.
33. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Vol. 46, Intensive Care Medicine. Springer; 2020. p. 1339–48.
34. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Vol. 2, Kidney International Supplements. Nature Publishing Group; 2012. p. 1–138.
35. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229).
36. Husain-Syed F, Ricci Z, Brodie D, Vincent JL, Ranieri VM, Slutsky AS, et al. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: from native to artificial organ crosstalk. Vol. 44, Intensive Care Medicine. 2018.
37. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. New England Journal of Medicine. 2020 Apr

16;382(16):1564–7.
38. World Health Organization. Infection prevention and control during health care when COVID-19 is suspected: Interim guidance. . Geneva; 2020.

ABBREVIATIONS

1. AKI=acute kidney injury.
2. Anti-Xa=anti-factor Xa.
3. aPTT=activated partial thromboplastin time.
4. CRRT=continuous renal replacement therapy.
5. CVVHD=continuous veno-venous haemodialysis.
6. CVVHDF=continuous venovenous haemodiafiltration.
7. ECCO2 R=extracorporeal carbon dioxide removal.
8. ECMO=extracorporeal membrane oxygenation.
9. HCO=high cutoff.
10. LMWH=low-molecular-weight heparin.
11. MCO=medium cutoff.
12. RCA=regional citrate anticoagulation.
13. RCTs=randomized controlled trials.