

# COVID-19 and Kidney Diseases in Indonesia

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## ABSTRACT

At the end of 2019, flu-like illness and pneumonia with an unknown cause first appeared in China. Later it is identified as Novel Coronavirus disease (COVID-19). This life-threatening disease spreads fastly worldwide and makes some disturbances in the health system, economy, and society. It affects many organs, especially the respiratory tract. Kidney involvement presents a lot of patients and increases morbidity and mortality. A recent study showed that abnormal kidney function was related to death in patients with COVID-19. This complication should be considered to prevent the worsening of the disease. The immune system plays a major role in this pathogenesis of disease and kidney problems. In this difficult situation, understanding COVID-19 and kidney diseases will help us to get proper management and prevention to solve the problem.

## Keywords:

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## INTRODUCTION

Coronavirus disease (COVID-19) is a life-threatening disease new highly infectious and may affect multiple organs such as the lungs, kidney, blood, digestive tract, and heart.<sup>1-3</sup> The first case emerged in China and rapidly spreading and declared a global pandemic.<sup>4</sup>

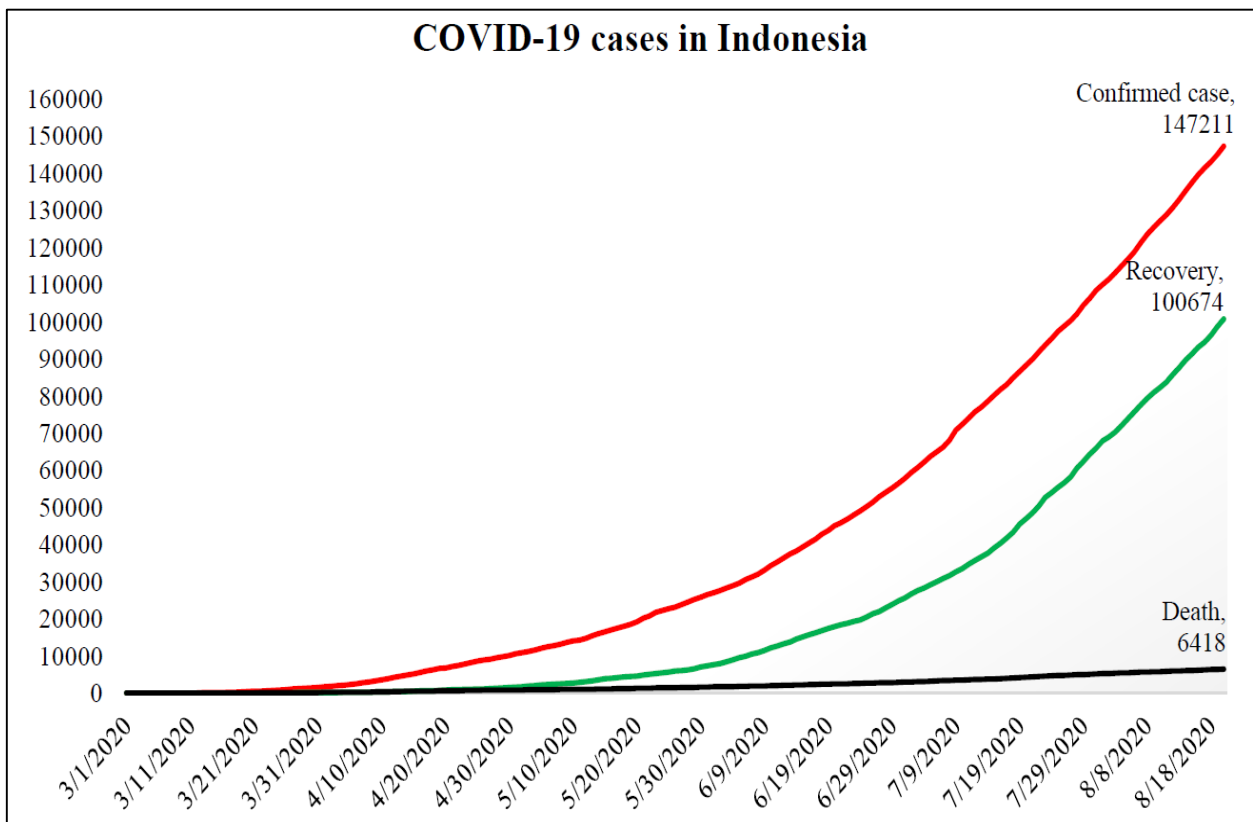
COVID-19 is a major threat and a pandemic all over the world. The infection affects all ages, including children moreover older people. Most of the infections are mild symptoms, manifesting as a flu-like illness.<sup>5</sup> COVID-19 with comorbidities tend to have worse illness and intensive care unit requirement. Kidney impairment may be found in this infection, and acute kidney injury (AKI) is an important predictor of death in COVID-19. The effect of this threat in those with chronic kidney disease (CKD) has a lack of study. Treatment of patients with dialysis (CKD-5D) who have been in contact with COVID-19 should follow the protocols to minimize the risk of spreading.<sup>4,6</sup>

## COVID-19

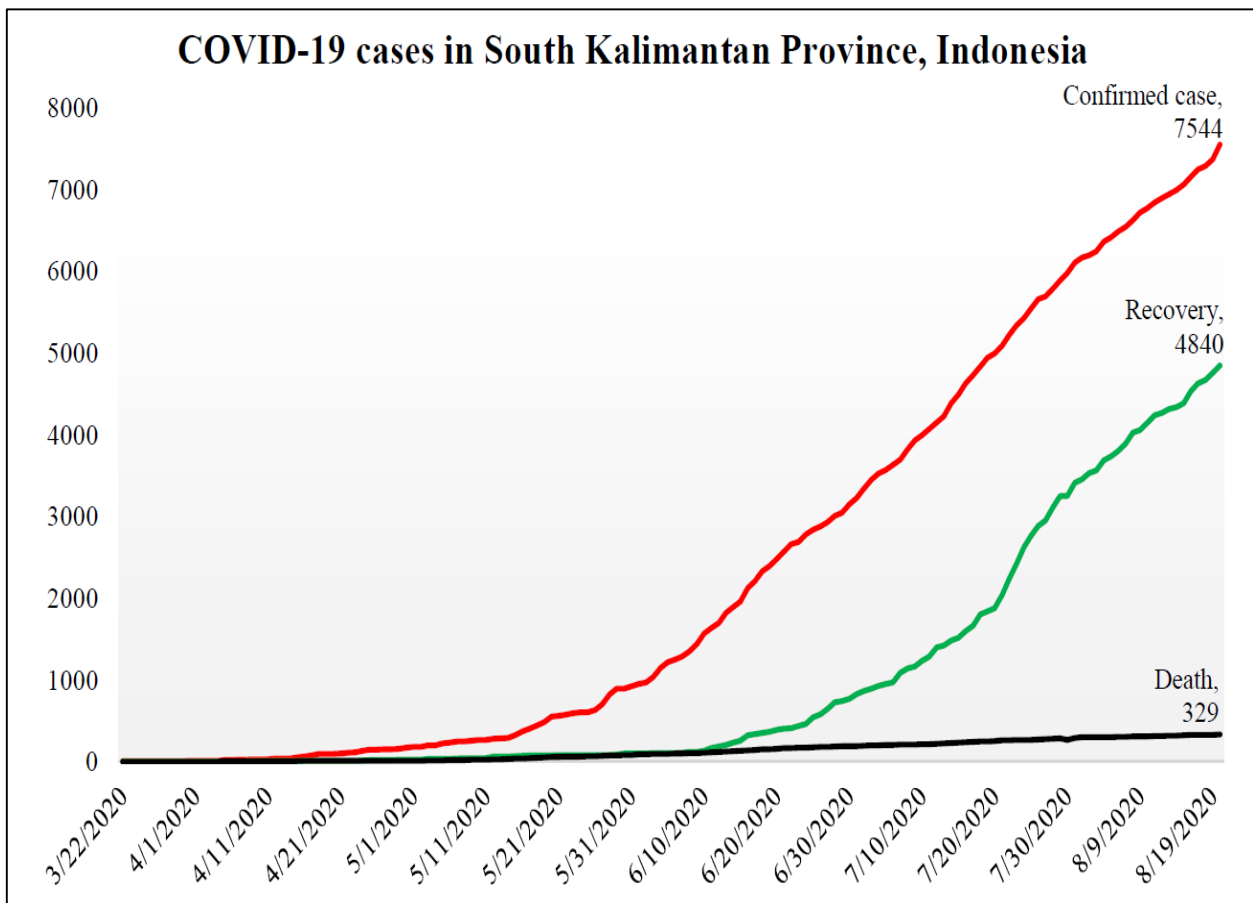
At the middle of August 2020, the WHO has confirmed more than 22 million cases and almost 800,000 deaths of COVID-19 worldwide. In Indonesia, it reaches almost 150,000 cases, and more than 6,400 deaths caused by COVID-19. Figure 1 shows the rapid growth of COVID-19 in Indonesia. Figure 2 shows the trend of COVID-19 in South Kalimantan, Indonesia until August 20<sup>th</sup>, 2020 with

more than 7,500 confirmed case and more than 300 deaths.<sup>3,7,8</sup> South Kalimantan mostly has wetland area, covered with abundant of water. It is necessary to protect the wetland area for community health system.<sup>9,10</sup>

SARS-CoV-2 is an RNA virus with envelope that infects humans and some animals. They are well-known to make some disturbances in the respiratory, enteric, neurological, renal and hepatic systems.<sup>12-14</sup> The outbreak in the late of 2019 in Wuhan, China has found pneumonia of unknown etiology. Work-up from lab investigations and deep sequencing studies found the etiology of a new strain of CoV.<sup>12</sup> The main form of transmission is now considered human-to-human transmission. The transmission occurs from the respiratory droplets spread through sneezing or coughing. The most common source of infection in people with symptoms. But, people who remain without symptoms may also transmit the virus.<sup>12</sup> COVID-19 may have asymptomatic manifestation to septic shock, respiratory failure and multiorgan dysfunction.<sup>15</sup> Most of the patients develop some symptoms include fever, cough, fatigue, and diarrhea. Patients with multiple comorbidities have a worse case fatality rate nearly 50%. Among 1 of 20 patients may progress a critical condition with respiratory failure, septic shock, cardiac injury, or multiple organ dysfunction.<sup>13,16</sup>



**Figure 1.** Trends of COVID-19 in Indonesia.<sup>11</sup>



**Figure 2.** COVID-19 cases in South Kalimantan Province, Indonesia

These comorbidities include diabetes, hypertension, respiratory disturbance, cardiovascular disease, and oncological complications. COVID-19 patients with sepsis are considered the worst of them all. The dysregulated host response to infection and inflammation may cause sequential organ failure.<sup>12,17,18</sup> Laboratory results of COVID-19 have some patterns include lymphocyte counts progressively decreased, elevated D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), and prothrombin time. CRP levels directly correlate with disease severity and progression. Other abnormal results showed cellular immune deficiency, renal injury, coagulation activation, myocardial injury, and hepatic injury.<sup>19</sup> Procalcitonin levels elevations are not common in COVID-19 patients and elevated procalcitonin levels may suggest other diagnosis such as bacterial pneumonia.<sup>12</sup> Some disturbances include high lactate, hyperbilirubinemia, acidosis, thrombocytopenia, and evidence of coagulopathy. They could have a serum lactate levels of >2 mmol/L. Patients with septic shock are accompanied by hypotensive conditions persistently although with adequate volume resuscitation.<sup>12,17,18</sup> COVID-19 may decrease the level of hemoglobin and neutrophil counts. Iron profile, CRP, LDH, and albumin increase significantly.<sup>20,21</sup> A recent study with homology modeling, and molecular docking reports that porphyrin may bind the ORF8 and surface glycoprotein. Some proteins including ORF3a, ORF10, and orflab proteins could damage the heme on the 1-beta chain to separate the iron to form the porphyrin. This condition will cause less hemoglobin can carry oxygen and carbon dioxide.<sup>21</sup> Anemia is one of the common symptoms in CKD, especially in dialysis patients. Patients with CKD 5D often followed by iron profile disturbances and need a further transfusion. This condition will increase ferritin levels. It will be difficult to distinguish the cause of iron disturbance in CKD-5D patients.<sup>22,23</sup> Management of COVID-19 includes isolation as the most effective method for COVID-19 prevention. There are no well-established anti-viral treatment or vaccine yet. COVID-19 treatment includes best supportive care. The preventive method must focus on infection prevention and control protocols optimization, and self-isolation. The WHO recommends avoiding close contact with patients and animals

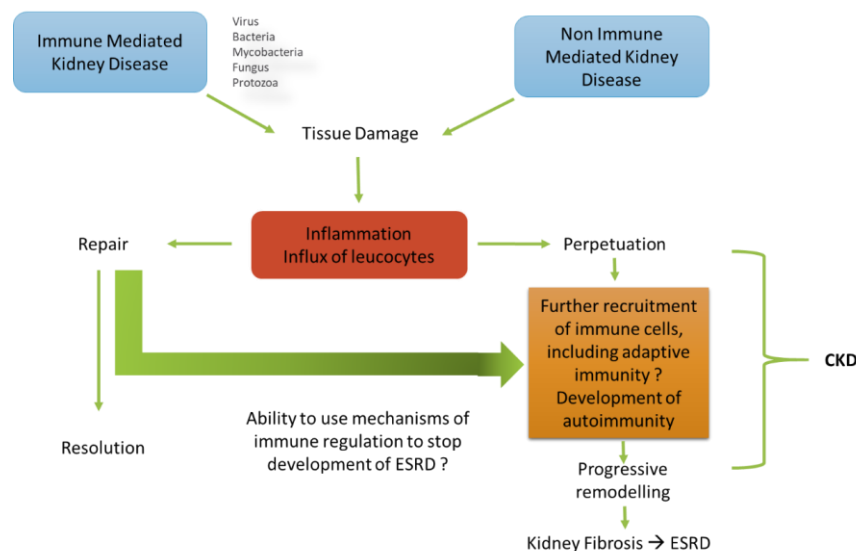
(domestic and wild).<sup>24</sup> To help prevent aerosol transmission, personal hygiene is very important.<sup>12</sup>

### COVID-19 and Kidney Disease

A study found that one third of patients with COVID-19 on the first day of hospitalization have massive albuminuria, and more than 60% get proteinuria during their treatment in the hospital. The increase of blood urea nitrogen is found in about 30% overall and more than 60% of death patients. The computed tomography (CT) scan of the kidneys may reveal density reduction with the sign of edema and inflammation.<sup>25</sup> Abnormal kidney function in patients with COVID-19 was related to a higher mortality rate. A recent prospective cohort study in China with more than 700 hospitalized patients with COVID-19 showed 16.1% of them died in hospital, around 40% of them had proteinuria and hematuria on the first admission. The serum creatinine increase incidence was 14.4% and blood urea nitrogen level increase was 13%. There were 13% patients with estimated glomerular filtration below 60 ml/min/1.73m<sup>2</sup>. According to the data, AKI occurred in around 5% of patients. AKI is an important risk factor for mortality in hospitalized patients with more than two-fold risk compared to without AKI. Further analysis showed that AKI stage 1 (hazard ratio (HR) 1.90; 0.76-4.76), AKI stage 2 (HR 3.51; 1.49-8.26), AKI stage 3 (HR 4.38; 2.31-8.31), proteinuria 1+ (HR 1.80; 0.81-4.00), 2+~3+ (HR 4.84; 2.00-11.70), and hematuria 1+ (HR 2.99; 1.39-6.42), 2+~3+ (HR 5.56; 2.58- 12.01) were risk factors for patient's death in hospital after some adjustments.<sup>26</sup> Patients with COVID-19 have some organ disturbances including the respiratory, liver, kidney and gastrointestinal tract similar to during the course of SARS in 2003. One of the most possible causes of the kidney involvement in some patients had a history of CKD. It is very important to consider AKI in hospitalized COVID-19 patients with an increase of serum creatinine.<sup>26</sup>

### Pathogenesis of kidney injury

The kidney disturbances mechanism in COVID-19 is not established yet. The immune system involvement in renal pathology including viral infection can be seen in Figure 3.<sup>4,27</sup>



**Figure 3.** The important role of the immune system in renal pathogenesis. CKD = chronic kidney disease; ESRD = end-stage renal disease. Adapted and modified from Tecklenborg, 2018.<sup>4,27</sup>

Kidney disease prevalence in COVID-19 is affected by many factors. Kidney disturbance due to COVID-19 may be caused by several mechanisms:

- The hypothesized mechanisms include sepsis with direct cellular damage or cytokine storm syndrome caused by the virus. Renal tubular cells express angiotensin-converting enzyme (ACE) and dipeptidyl peptidase (DPP). They are well-known as binding sites for SARS-CoV and MERS-CoV. Viral RNA in both infections had been detected in kidney tissue and urine. Recently, the urine sample of an infected patient successfully isolated SARS-CoV-2 in Zhong's lab in Guangzhou, suggesting COVID-19 had some impact to the kidney.<sup>4</sup>
- Virus may infect kidney organ which have some ACE2 receptor.<sup>28</sup> This receptor is responsible for virus invasion. ACE2 receptor can be found in proximal tubules, afferent arterioles and loop of Henle. The SARS-CoV-2 may induce cytopathic effects on kidney cells. PCR fragments support this statement of this virus in blood and urine of patients with COVID-19.<sup>4,29</sup> Urine of COVID-19 patient may contain some viral nucleic acid, it demonstrated that acute tubular necrosis can occur due to SARS-CoV-2 invasion to kidney tubules.<sup>30–32</sup> Human tissue RNA-sequencing data showed that the expression of ACE2 in urinary tracts was almost 100-fold higher than in respiratory tracts. Based on the data, coronavirus entering kidney cells through an ACE2-dependent pathway and may cause some kidney diseases.
- Pneumonia due to COVID-19 may cause hypoxia throughout the body include kidney organ. Hypoxia may induce some disruption due to increase blood viscosity and hypoxia-inducible transcription factor-dependent signaling mechanism and thrombosis. This condition will make the kidney function become worse.<sup>33</sup> The next hypothesize is the deposition of virus-induced specific immunological effector mechanisms or immune complexes of viral antigen may deteriorate the kidney. Kidney histopathology from patients with SARS showed a normal glomerular condition and no signs of deposits. Other possible mechanism is cytokines were induced by virus or mediators might impact indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis.<sup>26</sup>
- Inflammatory response in COVID-19 plays important role for multiple organs. COVID-19 patients have a higher level of some inflammatory mediators include interleukin-1 (IL-1), IL-6, TNF- $\alpha$  and interferon- $\alpha$  (IFN- $\alpha$ ). Cytokine storm syndrome is hypothesized as the possible cause of acute renal failure in some critically ill patients.<sup>34</sup>
- Hypercoagulability and thrombosis is one of the most important mechanisms in COVID-19. There is some elevation of D-dimer, prolongation of prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) in COVID-19 patients.<sup>35</sup> This condition may induce disseminated intravascular coagulopathy (DIC). They have pleiotropic effects with increasing production of proinflammatory cytokines. The host inflammatory reactions were triggering and described as inflammation and coagulation.<sup>36</sup> They make blockade the vascularization to kidney and make some injuries.<sup>35</sup>

### Management of patients on dialysis

Patients with COVID-19 in dialysis installation have some challenges features. Uremia conditions in CKD-5D patients are vulnerable to any infection and may risk a lot of variations in clinical severity and infectivity.<sup>37</sup> Dialysis installation with crowded people may increase the risk of infection transmission, including patients themselves, family members, healthcare staff, some facility workers, and all others.<sup>4</sup> Patients on dialysis need some COVID-19 prevention.<sup>38</sup> CKD-5D patients with COVID-19 had a lower incidence of lymphopenia and lower inflammatory cytokines serum levels.<sup>4,39,40</sup>

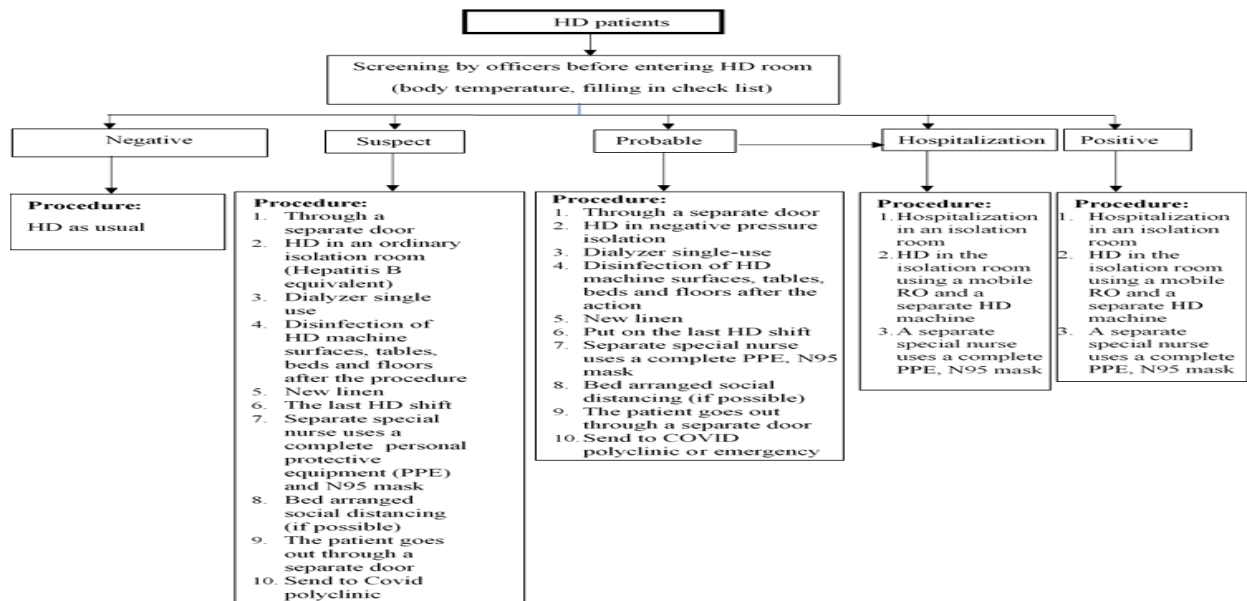
The American Society of Nephrology, Chinese Society of Nephrology, Taiwan Society of Nephrology, Indonesian Society of Nephrology have recently developed guidelines for dialysis units during the COVID-19 outbreak. Some key points of the recommendations are listed below.<sup>4,41,42</sup>

1. The dialysis facility needs to do entrance control, hand wash, body temperature, wearing of appropriate masks, recognition of people at risk of infection, environmental cleanliness, machine disinfection, good air, and ventilation conditions should be evaluated frequently.<sup>43</sup> In Banjarmasin, South Kalimantan, Indonesia we make some flow charts (Figure 4 and 5) for patients and caregiver in HD unit based on recommendations from Indonesian Society of Nephrology.<sup>42</sup>
2. The updated guidelines related to COVID-19 should be implemented to all medical staff. The training could be reached by online meeting or peer to peer approach.
3. A working team (include nephrologists, physicians, technicians, and dialysis nursing staff) need to receive training in COVID-19, the sign of infection at risk, infection prevention tools, and protocols from the government, hospital authority and academic society.
4. Medical staffs should have the self-awareness to their signs and symptoms. They should give the management the information in case they or their family have developed symptom(s) related to COVID-19.
5. History of dialysis patient, their family, medical staff, and colleagues at work should be reported and updated frequently. It is necessary to get information on travel, occupation, contacts, and cluster (TOCC).
6. Group activities should be limited (such as group studies, group rounds, and case discussions)
7. Before eat session, hands washed with flowing water, goggles, masks, and hats should be removed. To prevent the spread of droplets, talking during meals is not recommended. The medical staff needs to have a meal at different times to avoid transmission.<sup>43,44</sup>
8. Patients, their family or accompanying persons should be given some education related to hand washing before into the dialysis room. Patients and their accompanying person should use medical masks and forbid to bring any food during dialysis session.
  - a. Patients with confirmed or suspected COVID-19 should be treated in a negative-pressure isolation room.<sup>4,45,46</sup>
  - b. Dialysis shift and medical staff: it is not recommended to switch dialysis shifts and

- medical staff to prevent infection and cross-contamination.
- Transportation: Patients need to get personal transportation and specific routes. Public transport is not recommended.
  - Patients with fever symptoms should be considered for COVID-19 and should be arranged in the last shift of the day.
  - Dialysis machine: any device that may contact or related to patients or potentially

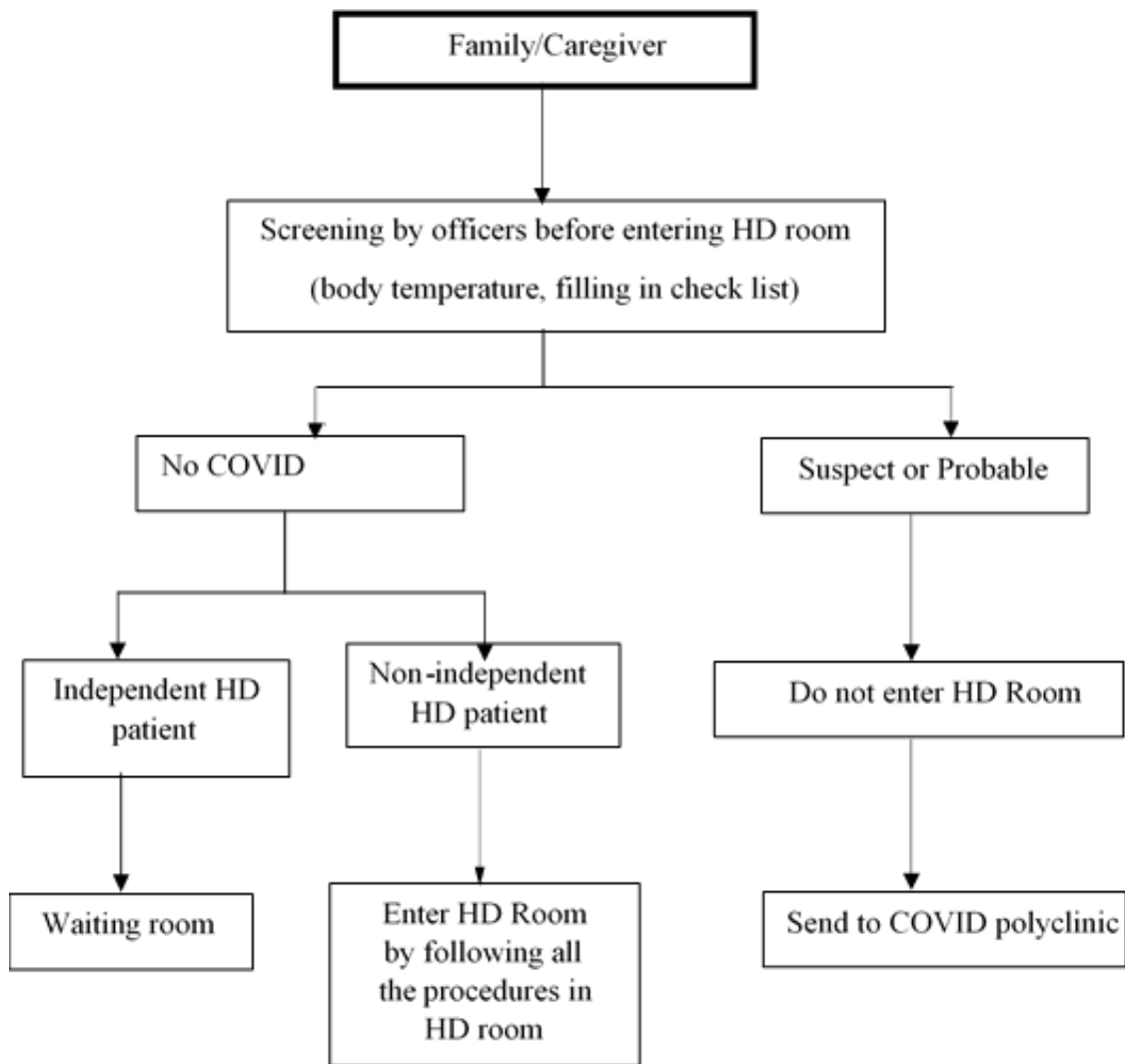
contaminated should be disinfected with standard operating procedure.

- Disinfection should be done immediately if a newly confirmed or highly suspected case of COVID-19 in dialysis centers is recognized. Areas should not be used until cleared and medical waste from confirmed or suspected patients with COVID-19 should be warned as infectious medical waste and disposed of properly.



**Figure 4.** Hemodialysis unit (HD) patient entrance flow in Ulin Hospital Banjarmasin. HD: hemodialysis, PPE: personal protective equipment, RO: reverse osmosis machine.





**Figure 5.** Hemodialysis unit (HD) family/caregiver entrance flow in Ulin Hospital Banjarmasin, Indonesia. HD: hemodialysis.

### Conclusion

COVID-2019 may impact multiple organs include respiratory, enteric, neurological, kidney and hepatic systems. The kidney disturbances pathogenesis from COVID-19 is not well understood yet. A recent study showed abnormal kidney function was related to death in patients with COVID-19. It is suggested that the immunopathology has an important role in this mechanism of kidney problems. Further study is needed to get better mechanisms, management, and prevention of COVID-19, especially in kidney diseases.

### Declaration of competing interest

The authors denied any conflicts of interest.

### Acknowledgements

This work is supported by the faculty of medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia. We thank our colleagues for their excellent contributions.

### Source of funding

No financial support was acquired.

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