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COVID-19-associated glomerulopathy and high-risk APOL1 genotype; Basis for a two-hit mechanism of injury? A narrative review on recent findings

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ABSTRACT

Kidney is one of the most common organs affected by coronavirus disease 2019 (COVID-19) after the respiratory and immune systems. Among the renal parenchymal components, the tubulointerstitial compartment is presumed to be the prime target of injury in COVID-19. The main mechanism of renal tubular damage by COVID-19 is considered to be indirect, i.e., cytokine-mediated injury. A proportion of infected individuals mount a strong inflammatory response to the virus by an exaggerated immune response of the body, namely cytokine storm. Sudden and massive release of cytokines may lead to serious systemic hyper-inflammation and renal tubular injury and inflammation resulting in acute renal failure. In addition, a number of cases of glomerulopathies, particularly collapsing glomerulopathy (CG) have been reported, predominantly in people of African ancestry, as a rare form of kidney involvement by SARS-CoV-2 that may originate from the background genetic susceptibility in this population complicated by the second hit of SARS-CoV-2 infection, either directly or indirectly. It is noteworthy that renal injury in COVID-19 could be severe in individuals of African origin due to the aforementioned genetic susceptibility, especially the presence of high-risk apolipoprotein L1 (APOL1) genotypes. Although the exact mechanism of kidney injury by SARS-CoV-2 is as yet unknown, multiple mechanisms are likely involved in renal damage caused by this virus. This review was aimed to summarize the salient points of pathogenesis of kidney injury, particularly glomerular injury in COVID-19 disease in the light of published data. A clear understanding of these is imperative for the proper management of these cases. For this review, a search was made of Google Scholar, Web of Science, Scopus, EBSCO and PubMed for finding English language articles related to COVID-19, kidney injury and glomerulopathy. From the information given in finally selected papers, the key aspects regarding glomerular involvement in COVID-19 were drawn out and are presented in this descriptive review.

Implication for health policy/practice/research/medical education:

Kidney injury is common in patients with coronavirus disease 2019 (COVID-19). Most of the cases are presumed to be due to tubular injury. However, cases of glomerulopathy, particularly collapsing glomerulopathy (CG), are being increasingly reported, predominantly in patients of African ancestry. Although the exact pathogenesis of CG in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still unsettled, accumulating evidence suggests this manifestation of kidney injury may be related to high risk APOL1 genetic susceptibility superimposed by a second hit by SARS-CoV-2, either directly or indirectly.

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Introduction

Coronavirus disease 2019 (COVID-19) is an emerging human infectious disease caused by a novel β -coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although it was first detected in Wuhan, China, in December 2019, it soon spread throughout the world and since then, over 13 million people around the world have been affected by the pandemic (1). While majority of cases are mild and self-limited presenting with upper respiratory tract symptoms, serious infection can occur in some individuals which can lead to serious complications and even death. The predominant organ involvement in individuals with SARS-CoV-2 is lung, which presents as a diffuse alveolar injury and pulmonary failure in severe cases (2). The virus may involve many other organs in severe cases, either directly or indirectly via a systemic hyperinflammatory response. A number of studies also reported acute renal dysfunction and other urinary abnormalities in the setting of moderate to severe COVID-19 disease (3). The precise mechanism of renal involvement and injury by SARS-CoV-2 has not yet been fully elucidated; but more and more data is accumulating on this topic. The most probable mechanisms are renal tubular damage due to cytokine storm, the direct cytopathic effect of the virus on tubular epithelial cells, and the glomerulopathy caused by immune mechanisms or direct cytopathic effects of the virus (4). For virus infectivity, the interaction of SARS viruses and angiotensin-converting enzyme 2 (ACE2) has been suggested as the prime factor. While the most frequent involved organ system is the pulmonary system presumably due to high expression of ACE2 in this system, involvement of other organs and body systems is not uncommon (4). Activation of angiotensin II pathway is also another possible mechanism of renal damage in COVID-19, since angiotensin II receptors have been suggested as a potential pathway contributing to viral infectivity and COVID-19-associated renal injury (5). Previous investigations showed that ACE2 is a membrane-bound peptidase, which acts as a protein ligand for SARS-CoV-2 binding in cell body, thereby permitting viral entrance and destruction of target organs. In fact, ACE2 is abundantly expressed in renal tissue, particularly in the proximal renal tubular cells. Notably, the tubular ACE2 expression in normal renal tissues is approximately one hundred times greater than that of the lungs (6). Likewise, there is a genetic deletion/insertion (D/I) polymorphism in intron 16 for activity of ACE1 for ACE concentration in tissues and blood. Therefore, the ACE polymorphism and vulnerability to COVID-19 can clarify the serious forms of SARS-CoV-2 among African American population versus the Caucasian population. In fact, the D allele of ACE1 is linked to diminished expression of ACE2 (7).

In this review, we briefly describe the most recent studies on COVID-19-associated glomerulopathy in addition to overall mechanisms of renal impairment in this disease.

Methods

For this review, we searched the following international databases; Google Scholar, Web of Science, Scopus, EBSCO and PubMed for finding English language articles related to COVID-19 and kidney injury from 1st January 2020 till 30th September 2020. The keywords included COVID-19, acute kidney injury, glomerulopathy, collapsing glomerulopathy, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), acute renal injury, angiotensin-converting enzyme 2, acute renal failure, cytokine storm, APOL1 genotype, and proteinuria/hematuria. All original and review articles and case reports relevant to this topic directly or indirectly were retrieved and carefully studied. From the information given in these papers, the following aspects were drawn out and presented in this narrative review for continued medical education (CME) of nephrology and nephropathology community. Figure 1 depicts the study methodology and strategy used to obtain data for this review.

Acute kidney injury in SARS-CoV-2

During the past few months of SARS-CoV-2 pandemic, numerous studies have reported that acute kidney injury occurs with wide incidence rate varying from 0.1% to 29% of hospitalized individuals (6). These studies showed that renal damage is reasonably frequent in this disease and contributes to the increased morbidity

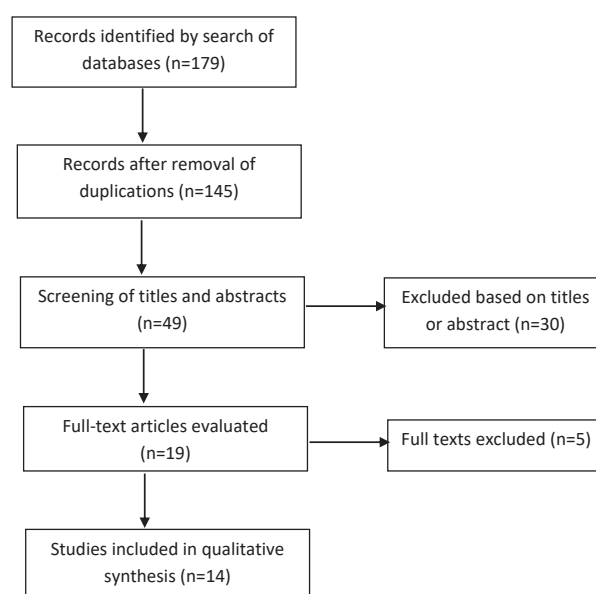


Figure 1. Flowchart showing the study strategy and methodology used to obtain data for this review.

and mortality in affected patients (2). Renal damage is characterized clinically by the presence of proteinuria (~44%), hematuria (~27%), and elevated plasma urea and creatinine (2,6). A study from China showed that 15.5% of COVID-19 patients had some evidence of renal involvement, while 3.2% of them developed acute renal injury during hospitalization (8). Both acute kidney injury and proteinuria are associated with increased mortality (9). While, acute tubular injury has been suggested as the most probable cause of renal disturbance; it does not explain proteinuria, which could be massive in some cases, and also hematuria (9). Studies have also shown that baseline chronic kidney disease (CKD) or pre-existing acute renal impairment is associated with increased mortality (4,9). Renal tropism of this virus was detected by viral RNA in various renal structures of individuals who died from SARS-CoV-2, inclusive of glomeruli (3). In a more recent meta-analysis of five relevant studies and 964 COVID-19 positive patients, the cumulative event rate of acute renal failure was 7.1% (95% confidence interval [CI]: 1.8%–24.5%, $P < 0.001$, $I^2 = 92.4$) (10).

Acute renal impairment in COVID-19 seems to develop from the interplay of several factors (Figure 2). To cite an example, fluid imbalance can lead to pre-renal acute renal failure, since recent data showed that 11% of SARS-CoV-2 positive individuals develop nausea, vomiting, or diarrhea as a manifestation of gastrointestinal disturbance in this illness (11). However, the main mechanism which explains renal damage by COVID-19 is cytokine-mediated tubulointerstitial injury. A group of infected individuals develop a strong inflammatory phase of the disease by an exaggerated response of the body, named cytokine storm, leading to significant lung and systemic inflammation,

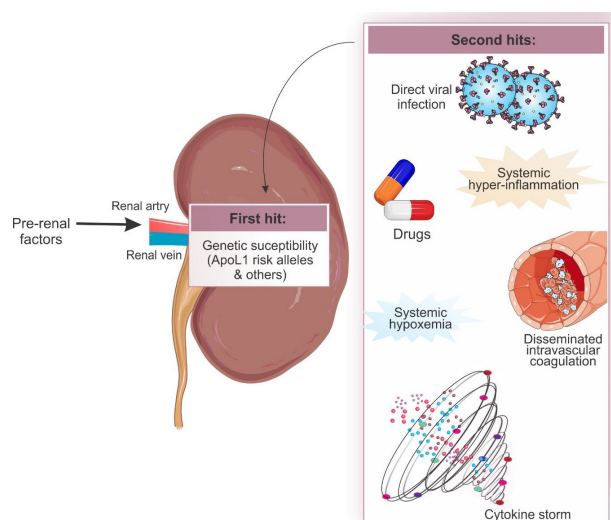


Figure 2. Schematic diagram showing interplay of first and second hits in causing kidney injury (Not shown are background chronic kidney disease or concurrent kidney disease associated with lesions of COVID-19 infection).

which may be fatal. Cytokines are small molecules, which normally act as inflammatory mediators in the fight of immune system against infections. However, the abrupt, massive release of cytokines and chemokines such as IL-6, IL-21, IL-8, IL-1 β , TNF- α , CCL-2, -3, -5 may lead to serious systemic inflammation and multi-organ damage (12). In an attempt to kill and overcome SARS-CoV-2 virus, the resultant inflammatory response can destruct normal tissue, including renal parenchyma, particularly the renal tubular epithelial cells (13). Additionally, there may be rapid viral replication, viral-mediated ACE2 down-regulation, cellular injury and shedding, leading to marked endothelial and epithelial cell loss and increased vascular permeability. These events trigger the production and release of chemokines and pro-inflammatory cytokines, which cause direct renal injury via apoptosis of kidney tubular epithelial cells (13). Thus, altered kidney function is an initial indicator of a hyper-inflammatory state; hence, assessment of renal function should be performed in all patients with COVID-19 (14). Furthermore, low concentration of oxygen in the circulation, due to pneumonia, could be another possible mechanism in causing renal impairment in COVID-19 infection (13). Other implicated factors for renal injury include diarrhea, disseminated intravascular coagulation, systemic hypotension, cardiac insufficiency, and dehydration in seriously ill cases infected with SARS-CoV-2. These conditions, in particular, intensify renal impairment in elderly with pre-existing diseases such as cardiovascular disease, diabetes or malignancy (15). Moreover, the acute viral myocarditis and cardiomyopathy could lead to hypotension and kidney hypoperfusion, resulting in reduction of glomerular filtration rate (7). Likewise, skeletal muscle damage, which has been detected in 19.3% of SARS-CoV-2 cases, leads to rhabdomyolysis, which can result in toxic renal tubular injury. Furthermore, use of contrast agents also elevates the risk of tubular toxicity. Other etiological factors consist of use of non-steroidal anti-inflammatory drugs, some antibiotics or antiviral agents, high dose of vitamin C particularly in elderly individuals and patients with underlying kidney disease (12,15). Studies regarding the long-term prognosis of acute kidney injury in COVID-19 patients are scarce and in progress. In previous studies, acute renal impairment was an independent risk factor for increased mortality. In addition, de novo proteinuria and hematuria were also independent predictors of increased mortality (5,16).

COVID-19-associated collapsing glomerulopathy

A small number of individual case reports and small case series, mostly from USA or Europe, have been published on glomerular involvement in COVID-19 infection predominantly in African American people (1-4,16-

23). The prevalent glomerulopathic lesion noted is that of collapsing glomerulopathy (CG). CG is an unusual form of FSGS, which has been previously described in individuals infected with human immunodeficiency virus type 1 (HIV-1) (17). The first case was reported by Kissling et al, in which a 63-year-old black male patient with COVID-19 infection developed oliguria and rapidly developing acute kidney injury (KDIGO stage 3) during hospitalization. The patient also had past medical history of high blood pressure that was under treatment. In the kidney biopsy, they detected morphologic lesion resembling CG. Immunofluorescence study was non-contributory. Electron microscopy showed podocyte vacuoles containing abundant spherical particles indicative of viral inclusion bodies resembling SARS-CoV-2. They concluded that CG, could be a consequence of direct viral effect on podocytes, possibly connected to the spectrum of coronavirus-related kidney involvement. There was no evidence of hilar variant of FSGS, which might be secondary to long-standing hypertension (23).

High-risk APOL1 genotype and COVID-19-associated collapsing glomerulopathy

More recently, Magoon et al (4), reported two African American cases who presented with AKI in the setting of COVID-19 infection. Kidney biopsy specimens showed CG along with the presence of acute tubular injury. Importantly, both cases were homozygous for Apolipoprotein L1 (APOL1) (4). Magoon et al could not detect viral particles in biopsy specimens in their patients. Therefore, a direct cytopathic damage was not envisaged to be the main mechanism of glomerular injury in these cases. It is possible that the COVID-19 infection acted as a second hit in genetically susceptible subjects due to APOL1, in the development of collapsing FSGS (4).

CG is a severe form of diffuse podocytopathy caused by various pathophysiological mechanisms including a number of viral infections like parvovirus B-19, HIV or cytomegalovirus, and some other agents like drugs, for example, interferon (IFN) or pamidronate. Su et al reported renal histopathologic findings in the first ever detailed pathologic analysis of 26 postmortem specimens of individuals who died of respiratory failure due to COVID-19 disease. They demonstrated diffuse renal proximal tubular damage with loss of brush borders, non-isometric vacuolization of tubular epithelial cells and even frank necrosis. Occasional hemosiderin granules and pigment casts were also noted. There were prominent red blood cell aggregates in peritubular capillaries obstructing the capillary lumens. In their series, there was not prominent and specific immune complex deposition, which ruled out the immune-mediated injury as the principal mode of injury. There were no features of

vasculitis or thrombosis. However, ultrastructural examination showed viral inclusions in cell cytoplasm, mostly in proximal renal tubular epithelial cells and less commonly in distal tubular cells. They also found viral inclusions in podocytes (18). Larsen et al described kidney biopsy and the clinical course of a female African American patient affected by COVID-19, who presented with constitutional syndrome in addition to proteinuria, hematuria and renal failure. Patient also had a past medical history of diabetes and hypertension. However, renal biopsy showed only morphologic aspects of collapsing FSGS without pathologic findings of diabetic kidney disease. Their case was homozygous for the G1 risk allele (rs73885319) of APOL1. This, therefore, represented an aggressive APOL1-related collapsing FSGS triggered by SARS-CoV-2-related cytokine storm (2). Yet, another case of collapsing FSGS in a 46-year-old West African man with SARS-CoV-2 infection was reported by Peleg et al (16). This case was also homozygous for G1 allele of APOL1 gene. Particularly, lung involvement was mild in this case, however acute renal failure was significant and mandate kidney replacement therapy. However, ISH (in-situ hybridization) for SARS-CoV-2 performed on formalin-fixed paraffin embedded kidney tissue sections was negative for the receptor binding domain of the spike protein of the virus. In contrast, Lazareth et al reported a patient of a 29-year-old renal transplant patient with sub-Saharan origin, who presented with acute renal injury and proteinuria following COVID-19 infection. Renal graft biopsy showed morphologic lesions of CG while genotyping for two risk alleles of APOL1 gene showed low-risk G0/G2 alleles of the kidney donor. In another case report, Malhotra et al presented a 64-year-old African American case with history of CKD stage 3 and controlled HIV who developed AKI with worsening azotemia after he was treated for ARDS in result of SARS-CoV 2 and got total vitamin C dose 84 g as a part of his regimen for 1 week. His renal biopsy findings support the diagnosis of CG concomitant with oxalate nephropathy because of high dosage of vitamin C. The APOL-1 risk variants expressed heterozygous of wild type and G1 variants, which are regarded as low-risks for CG. These case reports suggested that CG might be promoted by COVID-19 even in the presence of a low-risk APOL1 genotype (3, 19). Previous studies have shown that the APOL1 risk alleles are related to an increased proportion of newly diagnosed CG. More recent investigations suggest that renal expression of the APOL1 G1 and G2 risk variants could interfere with normal podocyte function. Besides, in the augmented inflammatory settings, Toll-like receptor agonists, IFNs and lipopolysaccharide substances, provoke APOL1 expression and its up-regulation (3). Furthermore, other cytokines and tumor necrosis factor (TNF) can also

stimulate APOL1 expression which causes severe damage to podocytes (20,21). The direct cytopathogenic effect of other viruses, like parvovirus B19, has been previously reported. This virus could involve renal tubular epithelial cells and podocytes provoking CG (17). Regarding HIV, a direct renal parenchymal infection including both the tubular epithelial cells and podocytes have been documented in the condition known as HIV-associated nephropathy (HIVAN). However, such evidence is not consistently observed in patients with coronavirus glomerular infection (6). In a previous study, Yeung et al showed that the Middle East respiratory syndrome-related coronavirus (MERS-CoV) was detected in podocytes and also in kidney tubular epithelium and was a cause of induced apoptosis (22). More recently, in 2 living individuals of COVID-19 disease, Couturier et al, reported collapsing FSGS with tubulointerstitial inflammation and fibrosis. However, using sensitive reverse transcriptase polymerase chain reaction techniques, they failed to find the virus in kidney tissue, blood or urine. They concluded that the renal lesions in COVID-19 are possibly not due to direct virus invasion of the renal tissue (17). Another case of CG was reported by Kissling et al in a COVID-19 positive 63-year-old black man who was developed AKI in the background of hypertension. Shortly after admission, the patient developed oliguria and rapidly progressive acute kidney injury. Kidney biopsy lesions of CG and ultra-structural study showed coronavirus-like particles in the cytoplasm of podocytes. Importantly, the patient was homozygous for APOL1 G1 variant (23). Other case reports showed different glomerular pathologies other than CG, for example, a report of de novo ANCA-associated glomerulonephritis in a 46-year-old South Asian COVID-19 positive male or report of a 65-year old Chinese female who developed kidney dysfunction with macroscopic hematuria and proteinuria during SARS-CoV-2 infection. She received a renal biopsy, which showed 2+ IgA mesangial deposits. Additionally, ultra-structural study showed electron-dense immune-type deposits in the mesangial area, while, there was no evidence of viral particles in the glomeruli (24). Similarly, Sharma et al reported two COVID-19 positive African American patients who developed acute renal impairment and proteinuria. The renal biopsies demonstrated collapsing FSGS associated with acute tubular injury and importantly, the presence of endothelial tubuloreticular bodies; however, the virus was not detected by electron microscopy. Both of their cases had APOL1 high-risk genotypes (25). The recent case report by Larsen et al showed the presence of tubuloreticular inclusions in their case report of collapsing FSGS related to COVID-19. However, other case studies did not detect the evidence of direct renal infection by COVID-19 RNA; nevertheless,

there is a possibility that the viral load was below the level for detection by the currently available techniques. Therefore, it is possible that collapsing FSGS may not be entirely the result of direct cytopathic effect of coronavirus. The other possible mechanisms may include the cytokine storm–induced damage, since the released cytokines may provoke apoptosis of glomerular cells (6). Hence, the development of collapsing FSGS in SARS-CoV-2 infection may be the consequence of immune system activation by chemokines and IFN more than the direct infection of glomerular cells (26). In another case report by Gaillard et al, a 79-year-old SARS-CoV-2 positive African male with renal failure was presented. Electron microscopy on renal biopsy showed diffuse foot process effacement and marked cytoplasmic vacuolization of podocytes. Interestingly, they could show viral particles. They also detected diffuse endothelial injury and swelling, in both glomerular and peritubular capillaries. The immune reaction to this virus may stimulate type 1 IFN response, which may account for the glomerular and endothelial damage (27). In a more recent case series of 10 renal biopsies who had clinical evidence of acute renal impairment and proteinuria in the background of COVID-19, Sharma et al showed presence of various degrees of acute tubular necrosis, and one patient had also myoglobin casts. Two of the patients had morphologic features of thrombotic microangiopathy, and another patient had pauci-immune crescentic glomerulonephritis. One of the cases had features of collapsing FSGS. Patients had mean age of 65 years, while five of them were black, three were Hispanic, and two were white. While, 8 individuals had significant acute renal impairment, all of them had proteinuria. Despite severe SARS-CoV-2 infection, they could not show the virus in biopsy samples of all 10 patients either by immunohistochemical or ultrastructural study (28).

Nlandu et al reported the first case of CG in a 48-year-old African man from Congo co-infected by COVID-19 and malaria. The patient achieved partial remission of proteinuria and partial improvement in kidney function. They did not test for APOL1 genotype due to non-availability of the test. They claimed that this was the first report of glomerulopathy in COVID-19 patients from Africa (29), they also did not look for direct viral infection in the kidney tissue.

Deshmukh et al reported the first case of CG in a 42-year-old Indian origin man with COVID-19 infection (30). They did find evidence of direct viral infection of podocytes on electron microscopy. However, they could not perform APOL1 genotyping as the patient was lost to follow-up. A summary of studies describing glomerulopathies in patients with COVID-19 infection is provided in Table 1.

Table 1. Summary of studies reporting collapsing glomerulopathy in patients with COVID-19 disease and kidney involvement

Authors	Type of study	Total No. of patients	Patients with CG or FSGS	Gender M/F	Race	ApoL1 alleles	Evidence of direct viral infection	Outcome	Remarks
Gupta et al ¹	CR	02	02	2/0	Indian/AA	Not done	Not found	1 improved 1 on Dx	
Larsen et al ²	CR	01	01	1/0	AA	Positive	Yes	Partial improvement	
Lazareth et al ³	CR	01	01	1/0	AA	Low risk	Not found	Partial improvement	Transplant patient
Magoon et al ⁴	CR	02	02	1/1	AA	Positive	Not found	Both Dx free 2 died	
Wu et al ⁶	CS	06	06	4/2	AA	Positive	Not found	2 Dx dependent 2 improved	
Peleg et al ¹⁶	CR	01	01	1/0	AA	Positive	Not found	Dx-dependent	
Couturier et al ¹⁷	CR	02	02	2/0	African	Positive	Not found	Both in partial remission	
Su et al ¹⁸	CS	26	02		Chinese	Not done	Yes	Not mentioned	pm study
Kissling et al ²³	LTE	01	01	1/0	AA	Not done	Yes	SCr 5.5 mg%	
Sharma et al. ²⁵	CR	02	02	1/1	AA	Positive	Not found	Both on Dx	
Gaillard et al ²⁷	Image	01	01	1/0	AA	Not done	Not found	Dx-dependent	
Sharma et al ²⁸	RC	10	01	0/1	AA	Not done	Not found	Dx free	
Nlandu et al ²⁹	CR	01	01	1/0	African	Not done	Not done	Partial improvement	
Deshmukh et al ³⁰	CR	01	01	1/0	Indian	Not done	Yes	Lost to follow-up	

Abbreviations: AA, African American; CR, case report; CS, case series; LTE, letter to editor; RC, rapid communication; Dx, dialysis; SCr, serum creatinine; pm, postmortem.

Conclusion

According to the above data, we can hypothesize that CG is a fulminant form of kidney injury by SARS-CoV-2 that may originate from genetic susceptibility complicated by the second hit of SARS-CoV-2 infection, affecting either directly or indirectly. It is noteworthy that renal injury in COVID-19 could be severe in individuals of African origin due to their genetic susceptibility, in the form of high-risk APOL1 genotypes or in lower risk heterozygous APOL-1 variants in the presence of overwhelming immune response.

Authors' contribution

Primary draft by MM, AP and SP. AD conducted the first edit, MM conducted the second edit. LM, SMK, PP and NA completed the paper and conducted further editions. AP and MM finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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