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Review

COVID-19 and diabetes: Knowledge in progress



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ABSTRACT

Aims: We aimed to briefly review the general characteristics of the novel coronavirus (SARS-CoV-2) and provide a better understanding of the coronavirus disease (COVID-19) in people with diabetes, and its management.

Methods: We searched for articles in PubMed and Google Scholar databases till 02 April 2020, with the following keywords: "SARS-CoV-2", "COVID-19", "infection", "pathogenesis", "incubation period", "transmission", "clinical features", "diagnosis", "treatment", "diabetes", with interposition of the Boolean operator "AND".

Results: The clinical spectrum of COVID-19 is heterogeneous, ranging from mild flu-like symptoms to acute respiratory distress syndrome, multiple organ failure and death. Older age, diabetes and other comorbidities are reported as significant predictors of morbidity and mortality. Chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying mechanisms of the association between diabetes and COVID-19. No conclusive evidence exists to support the discontinuation of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers or thiazolidinediones because of COVID-19 in people with diabetes. Caution should be taken to potential hypoglycemic events with the use of chloroquine in these subjects. Patient tailored therapeutic strategies, rigorous glucose monitoring and careful consideration of drug interactions might reduce adverse outcomes.

Conclusions: Suggestions are made on the possible pathophysiological mechanisms of the relationship between diabetes and COVID-19, and its management. No definite conclusions can be made based on current limited evidence. Further research regarding this relationship and its clinical management is warranted.

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1. Introduction

Coronaviruses are enveloped, positive single-stranded RNA viruses widely distributed in humans and animals worldwide [1]. Although most human coronavirus infections are mild, major outbreaks of two betacoronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, have caused deadly pneumonia, with mortality rates of 10% for SARS-CoV and 36% for MERS-CoV [2].

In December 2019, clusters of pneumonia cases of unknown etiology emerged in Wuhan, Hubei Province, China. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus as the causative agent, which was named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), and the disease it causes called COVID-19 [1,3]. Although SARS-CoV-2 has shown phylogenetic and clinical similarities with SARS-CoV, the novel coronavirus appears to have a higher transmissibility and lower case fatality rates [4]. On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern, and on March 11, the epidemic was upgraded to pandemic [5]. As of today (02.04.2020), 827,419 confirmed cases are officially reported in more than 200 countries or territories with 40,777 deaths [6].

We conducted a scoping review to provide a brief summary of the general characteristics of COVID-19, as well as a more detailed description and critical assessment of the association between this new infectious disease and diabetes. We hope this review can provide meaningful information for future research and ultimately contribute to better clinical management of patients with COVID-19 and diabetes.

2. Methods

A literature review was carried out to search for articles in PubMed and Google Scholar databases till 02 April 2020. The following keywords were used: “SARS-CoV-2”, “COVID-19”, “infection”, “pathogenesis”, “incubation period”, “transmission”, “clinical features”, “diagnosis”, “treatment”, “diabetes”, with interposition of the Boolean operator “AND”. We also retrieved the full text of the relevant cross references from the search results. Furthermore, we accessed the currently available scientific literature and recommendations in the WHO and United States Centers for Disease Control and Prevention (CDC) websites.

3. General characteristics of COVID-19

3.1. Incubation period

The incubation period is described as the time from infection to illness onset. In a study of 1099 patients from China with laboratory-confirmed symptomatic COVID-19, the median incubation period was four days (interquartile range, 2–7) [7]. Another study including 181 confirmed cases reported a median incubation period of approximately 5 days, and that symptoms would develop in 97.5% of infected individuals within 12 days [8]. Based on the incubation period of SARS-CoV and MERS-CoV, as well as observational data, the United States CDC has estimated that symptoms of COVID-19 will usually develop within 2–14 days after exposure. Therefore, fourteen days has been the time applied internationally for monitoring and restricting the movement of healthy individuals (quarantine period) [9].

3.2. Modes of transmission

Most initial COVID-19 patients had a direct contact history with a local Chinese seafood and wildlife market, suggesting a common-source zoonotic exposure as the main mode of transmission [10]. Findings from virus genome sequencing analysis have pointed out that SARS-CoV-2 and bat coronavirus (bat CoV) might share the same ancestor, although bats are not for sale in this seafood market [11]. Later cases were reported among health care workers and others without exposure history of wildlife or visiting Wuhan, which indicated human-to-human transmission [10]. Currently, it is considered that the virus can be mainly transmitted through droplets, direct contact and aerosols. Droplets transmission may occur when respiratory droplets, produced when an infected person coughs or sneezes, are ingested or inhaled by individuals nearby (within about 6 feet). A subject can also get infected by touching a surface or object contaminated with the virus and subsequently touching his/her mouth, nose, or eyes [12]. Additionally, it has been shown experimentally that the virus can remain viable in aerosols for at least 3 h [13], and can be transmitted in closed environments if inhaled into the lungs [12]. Therefore, airborne transmission is a possibility during aerosol generating procedures, e.g., endotracheal intubation, bronchoscopy, non-invasive positive-pressure ventilation, tracheostomy, cardiopulmonary resuscitation, etc [14]. Although viable virus has been identified in fecal swabs, the fecal-oral route does not appear to be a driver of COVID-19 transmission [11].

3.3. Period of infectivity

It is uncertain how long an individual with COVID-19 remains infectious. The period of infectivity is often assessed indirectly by detection of viral RNA from respiratory specimens. However, viral RNA does not necessarily confirm the presence of infectious virus. Higher viral loads have been detected soon after symptom onset, suggesting that transmission may be more likely to occur in the earlier stages of infection [15]. The viral shedding duration seems to vary according to the disease severity. It has been found that around 90% of patients with milder symptoms had a negative viral RNA test on nasopharyngeal swabs by day 10 post-onset, while the test remained positive for a longer time in all severe cases [16]. On the other hand, it has been reported that the viral load detected in asymptomatic patients was similar to that in symptomatic subjects [15]. Indeed, transmission from asymptomatic carriers or individuals within the incubation period has been described [17]. Nevertheless, the extent to which this occurs remains to be determined.

3.4. Demography and clinical characteristics

Even though all age groups have been affected by COVID-19, the median age appears to be around 47–59 years, and usually higher among severe cases and non-survivors. No specific gender bias seems to exist for the contamination with the virus, but men tend to have a higher propensity of the cases [7,18,19]. Fewer cases have been identified among children

and infants. In a large Chinese report including 72,314 patients, only 2% of those infected were younger than 20 years old [20].

The clinical spectrum of COVID-19 can be very heterogeneous. Most adults and children present mild flu-like symptoms, but some may rapidly develop acute respiratory distress syndrome (ARDS), respiratory failure, arrhythmias, acute cardiac injury, shock, multiple organ failure and death [1,18]. The most commonly reported symptoms are fever, cough, fatigue, sputum production and shortness of breath. However, headache, upper respiratory symptoms (e.g., sore throat and rhinorrhea) and gastrointestinal symptoms (e.g., nausea and diarrhea) occur less often [1,7,18]. Although not described in the initial Chinese studies, smell and taste disorders (e.g., anosmia and dysgeusia) have also been found frequently in patients with COVID-19 in Italy [21].

In laboratory examination results, most patients have normal or decreased white blood cell counts, particularly lymphocytopenia [7]. However, in severe patients, the neutrophil count, inflammatory markers, D-dimer, blood urea, and creatinine levels are generally higher, with further decreased lymphocyte counts [1]. Chest computed tomography (CT) most commonly shows ground-glass opacifications with or without consolidative abnormalities. They are also more likely to be bilateral, have a peripheral distribution and involve the lower lobes [7,22]. While some confirmed cases may present normal CT images [11], abnormalities have also been identified prior to the development of symptoms in some patients [22].

3.5. Diagnosis

The diagnosis of COVID-19 cannot be made without microbiologic analysis. Patients who meet the criteria discussed below should undergo testing for SARS-CoV-2, in addition to testing for other respiratory pathogens (e.g., influenza, respiratory syncytial virus, etc). Since testing for COVID-19 in suspected cases is limited owing to inadequate capacity, local health authorities may introduce specific criteria for priority cases [23]. Although many laboratory tests have been developed, real-time fluorescence (RT-PCR) has been the current standard diagnostic method for diagnosis of COVID-19, by detecting the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretions of the lower respiratory tract samples [23,24].

3.5.1. Criteria for suspicion and testing

Community surveillance should be introduced in all countries in order to register the new cases of COVID-19 and map the transmission route. According to the WHO and other literature, the following is recommended [23,25]:

3.5.1.1. Preliminary symptoms for observations. Individuals with new onset fever and/or respiratory tract symptoms (e.g., cough, dyspnea) or patients with severe lower respiratory tract illness, without any clear cause and without any history of close contact with a confirmed COVID-19 patient or have travelled to an area of community transmission.

3.5.1.2. *Tests should be performed depending on resources.* Subjects with new onset fever and/or respiratory tract symptoms (e.g., cough, dyspnea) or patients with severe lower respiratory tract illness, who have been in contact with COVID-19 patients or travelled within 14 days to a location where community transmission of SARS-CoV-2 is present. Furthermore, patients older than 60 years of age, as well as those with underlying conditions like diabetes, hypertension, cardiovascular diseases (CVDs), chronic renal disease, cancer and immunocompromising conditions, who develop symptoms of fever, cough and/or dyspnea should be prioritized for testing.

3.5.1.3. *Must be tested.* Persons in close contact (within 2 m) with a SARS-CoV-2 infected individual for a prolonged period or in direct contact with infectious secretions while not wearing personal protective equipment.

3.6. COVID-19 and comorbidities

Although the pathophysiological mechanisms are still not understood, it has been observed that most severe and fatal cases with COVID-19 have occurred in the elderly or in patients with underlying comorbidities, particularly CVDs, diabetes mellitus, chronic lung and renal disease, hypertension, and cancer [7,20,26,27].

One Chinese meta-analysis including 1527 patients showed that the most prevalent cardiovascular metabolic comorbidities with COVID-19 were hypertension (17.1%, 95% CI 9.9–24.4%) and cardio-cerebrovascular disease (16.4%, 95% CI 6.6–26.1%), followed by diabetes (9.7%, 95% CI 6.9–12.5%). In this report, patients with diabetes or hypertension had a 2-fold increase in risk of severe disease or requiring intensive care unit (ICU) admission, while those with cardio-cerebrovascular disease had a 3-fold increase [28]. In a subset of 355 patients with COVID-19 in Italy who died, the mean number of pre-existing underlying conditions was 2.7, and only 3 subjects did not have any comorbidity [29].

It has been consistently reported that, in addition to pneumonia, SARS-CoV-2 may cause damage to other organs including the heart, liver and kidneys [1,18]. Therefore, full attention should be paid to the treatment of the original comorbidities, especially in older patients with already severe underlying conditions.

4. Association between COVID-19 and diabetes

4.1. Diabetes and Infection: General considerations and potential mechanisms

Diabetes is one of the leading causes of morbidity and mortality throughout the world. The condition is associated with several macrovascular and microvascular complications, that ultimately impact the overall patient's survival [30]. A relationship between diabetes and infection has long been clinically recognized [31]. Infections, particularly influenza and pneumonia, are often common and more serious in older people with type 2 diabetes mellitus (T2DM) [32,33]. Neverthe-

less, the evidence remains controversial regarding whether diabetes itself indeed increases susceptibility and impacts outcomes from infections, or the cardiovascular and renal comorbidities that are frequently associated with diabetes are the main factors involved [34].

Diabetes and uncontrolled glycaemia were reported as significant predictors of severity and deaths in patients infected with different viruses, including the 2009 pandemic influenza A (H1N1) [35], SARS-CoV [36] and MERS-CoV [37]. In the current SARS-CoV-2 pandemic, some studies did not find a clear association between diabetes and severe disease [19,38]. However, other reports from China [7,20] and Italy [29] showed that older patients with chronic diseases, including diabetes, were at higher risk for severe COVID-19 and mortality.

Scarce data exist regarding glucose metabolism and development of acute complications of diabetes (e.g., ketoacidosis) in patients with COVID-19. Infection of SARS-CoV-2 in those with diabetes possibly triggers higher stress conditions, with greater release of hyperglycemic hormones, e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose variability [39]. On the other hand, a retrospective study from Wuhan reported that around 10% of the patients with T2DM and COVID-19 suffered at least one episode of hypoglycemia (<3.9 mmol/L) [40]. Hypoglycemia has been shown to mobilize pro-inflammatory monocytes and increase platelet reactivity, contributing to a higher cardiovascular mortality in patients with diabetes [41]. Yet it remains largely unknown how exactly the inflammatory and immune response occurs in these patients, as well as whether hyper- or hypoglycemia may alter the SARS-CoV-2 virulence, or the virus itself interferes with insulin secretion or glycemic control. Furthermore, the impact of usual diabetes drug treatment on COVID-19 outcomes, as well as therapeutic approaches for COVID-19 on glucose regulation remains unspecified.

Diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect our response to pathogens [34]. Hyperglycemia and insulin resistance promote increased synthesis of glycosylation end products (AGEs) and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation [34,42]. This inflammatory process may compose the underlying mechanism that leads to a higher propensity to infections, with worse outcomes thereof in patients with diabetes [34].

Several defects in immunity have been associated with hyperglycemia, even though the clinical relevance of some *in vitro* disturbances are still not fully understood [43]. Poorly controlled diabetes has been linked to inhibited lymphocyte proliferative response to different kinds of stimuli [44], as well as impaired monocyte/macrophage and neutrophil functions [34]. Abnormal delayed type hypersensitivity reaction [43] and complement activation dysfunction [45] have also been described in patients with diabetes. *In vitro* studies have shown that pulmonary epithelial cells exposure to high glucose concentrations significantly increases influenza virus infection and replication, indicating that hyperglycemia may enhance viral replication *in vivo* [46]. In animal models, struc-

tural lung changes have been related to diabetes, such as augmented vasculature permeability and collapsed alveolar epithelium [47]. On the other hand, patients with diabetes generally present a significant reduction in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), which is associated with raised plasma glucose levels [48].

4.2. Aspects of SARS-CoV-2 pathogenesis and potential implications for clinical management of patients with COVID-19 and diabetes

Patients with COVID-19 commonly show on admission lymphocytopenia, and to a lesser extent thrombocytopenia and leukopenia, which are more prominent among those with severe disease [7]. Further, elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and C-reactive protein, as well as increased coagulation activity, marked by higher d-dimer concentrations, were also associated with severity [7,26]. In T2DM, besides the marked inflammatory process previously discussed, an imbalance between coagulation and fibrinolysis takes place, with increased levels of clotting factors and relative inhibition of the fibrinolytic system. Both insulin resistance and T2DM are associated with endothelial dysfunction, and enhanced platelet aggregation and activation. These abnormalities favor the development of a hypercoagulable pro-thrombotic state [49]. Additionally, atherosclerosis, vascular inflammation and endothelial dysfunction are also part of the pathogenesis of other chronic conditions, e.g., hypertension and CVDs [42]. Animal studies involving SARS-CoV reported that older age was related to defects in T-cell and B-cell function and excess inflammation markers. Thus, T2DM alone or in association with older age, hypertension and/or CVDs might contribute to a deficient control of SARS-CoV-2 replication and more prolonged proinflammatory response, potentially leading to poor outcomes [26].

Viral entry into the host cells is a fundamental component of cross-species transmission, particularly for the coronaviruses (CoVs). Upon exposure of the host to the virus, all CoVs, through a Spike protein, bind to cells that express specific receptors. After binding to the target cells, the host-cell protease cleaves the spike, which allows the virus to enter and replicate [50]. The angiotensin-converting enzyme 2 (ACE2) has been identified as one of the main receptors for both SARS-CoV [51] and SARS-CoV-2 [50]. ACE2 is widely expressed on the respiratory tract, heart, kidneys, intestines, cerebral neurons, endothelium of arteries and veins, immune cells and pancreas [2]. A Chinese study compared 39 SARS-CoV patients without previous diabetes, who did not receive steroid treatment, with 39 matched healthy siblings and showed that 20 of the 39 SARS-CoV patients developed diabetes during hospitalization. Since immunostaining for ACE2 was strong in the pancreatic islets, it was suggested that SARS-CoV might have damaged islets and caused acute insulin dependent diabetes mellitus [52]. Therefore, although further evidence is needed, pancreatic damage may also be present in COVID-19 patients, possibly contributing to worse outcomes in subjects with diabetes.

Previous studies have reported decreased mortality and endotracheal intubation in patients with viral pneumonia

who were in continued use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [53,54]. These medications are postulated to have significant immunomodulatory effects [55] and reduce pulmonary and systemic inflammatory response by decreasing cytokines [53,54]. They are commonly used by those with diabetes and hypertension [56], therefore, their impact on the clinical course of COVID-19 has been widely debated. Considering that ACE2 is a functional receptor for SARS-CoV-2 and its levels can be increased by ACEIs and ARBs, it has been argued that these drugs might affect negatively the outcome of COVID-19 patients [57]. On the contrary, some have advocated that ACEIs and ARBs might rather be beneficial [58]. SARS-CoV infection and the virus Spike protein reduce ACE2 expression. Mice injected with SARS-CoV Spike presented worsened acute lung failure, which could be attenuated by blocking the renin-angiotensin pathway [59]. Nevertheless, a retrospective analysis performed on 112 patients with COVID-19 and CVD did not show a significant difference in the proportion of ACEI/ARB medication between survivors and non-survivors [60]. Similar to ACEIs and ARBs, ibuprofen [61] and thiazolidinediones [62] can also result in increased levels of ACE2, thus generating questions regarding the safety of these drugs in patients with COVID-19.

Although diabetes has been associated with worse outcomes in COVID-19 patients, the susceptibility to SARS-CoV-2 infection may not be higher in people with diabetes. According to several studies, the prevalence of diabetes in people infected with the virus is about the same as in the general population, even slightly lower [28,63]. A meta-analysis of 12 studies describing data from 2,108 Chinese patients with COVID-19 reported a diabetes prevalence of 10.3% [63], which was similar to the national prevalence of 10.9% reported in 2013 [64]. An Italian study conducted among 146 patients with confirmed SARS-CoV-2 infection at the University Hospital of Padova found an equivalent pattern. The prevalence of diabetes in these patients was 8.9% (mean age 65.3 years), while it was 11.0% among people aged 55–75 years (mean age 65 years) from the same region in 2018 [65]. Although under-reporting may be an issue to consider, potential biological mechanisms should not be disregarded. It has been shown that dipeptidyl peptidase-4 (DPP-4) is the primary receptor of MERS-CoV [2]. Since DPP-4 inhibitors are commonly applied in the treatment of diabetes worldwide, future research should explore whether DPP-4 may also act as receptor for SARS-CoV-2, thus contributing to a potential protective effect of these drugs against COVID-19 [63,66].

So far, no anti-SARS-CoV-2 drug or vaccine has been officially approved for COVID-19 treatment [67]. Several clinical trials are in progress to assess the safety and efficacy of potential treatment alternatives, including remdesivir, tocilizumab, lopinavir/ritonavir, ribavirin, interferon, chloroquine phosphate, arbidol, among others [68]. One promising pharmacological option of relevance for patients with diabetes is chloroquine and its hydroxy-analogue hydroxychloroquine. Widely used for malaria and autoimmune diseases, chloroquine has also been reported as a potential broad-spectrum antiviral drug. Although the efficacy and safety of chloroquine for COVID-19 treatment remain unclear, a recent study showed that the drug was highly effective in controlling

SARS-CoV-2 infection in vitro. In addition to its immunomodulatory and anti-inflammatory effect, chloroquine increases endosomal pH and interferes with the glycosylation of cellular receptors of SARS-CoV, thereby blocking viral infection [69]. Preliminary results from more than 100 patients included in a Chinese clinical trial showed that chloroquine was superior to the control group in shortening the disease course, inhibiting pneumonia exacerbation, promoting a virus negative conversion and radiological improvement without severe side effects [70]. On the other hand, several studies have reported that hydroxychloroquine improves glycemic control in decompensated, treatment-refractory patients with diabetes [71,72]. It has even been approved to treat T2DM in India as an add-on therapy for patients who do not achieve glycemic targets with two other oral glucose-lowering drugs [73]. Although inflammation is associated with impaired glucose control, the underlying mechanism of hydroxychloroquine's hypoglycemic effect remains unclear [71]. It has been described that chloroquine increases the C peptide response, potentially reflecting an improved pancreatic β -cell function [72]. Reduced intracellular insulin degradation and increased insulin accumulation have also been identified as possible effects of hydroxychloroquine in animals models [74]. Given the previously reported impact of chloroquine/hydroxychloroquine on glucose metabolism, caution should be taken when the drug is administered to patients with diabetes and COVID-19. A dose adjustment of the oral antidiabetic drugs and/or insulin might be necessary in order to prevent potential hypoglycemic events.

The effect of corticosteroids on COVID-19 is also under investigation [68]. Acute lung damage and ARDS are partly due to the host immune response. While corticosteroids suppress lung inflammation, they also inhibit immunity and pathogen clearance [75]. In SARS-CoV and MERS-CoV infections, pulmonary histology showed inflammation and diffuse alveolar damage [76]. Therefore, corticosteroids were broadly applied [77,78]. However, evidence did not show benefits, rather it was reported delayed viral RNA clearance or increased mortality and rate of complications, including diabetes, psychosis, and avascular necrosis [75]. The interim guidance from the WHO on clinical management of severe acute respiratory infection when SARS-CoV-2 infection is suspected advises against the use of corticosteroids outside clinical trials [79]. Considering the hyperglycemic effect [80] and the impact of these drugs on the immune response [75], special caution should be taken in patients with diabetes included in trials assessing the safety and efficacy of corticosteroids for COVID-19 [80].

No data is available regarding the most appropriate management of patients with diabetes infected by SARS-CoV-2, as well as patients with COVID-19 who develop glycemic decompensation. Rigorous glucose monitoring and careful consideration of drug interactions might attenuate worsening of symptoms and adverse outcomes. Although hyperglycemia is usually the main concern in this context, one should not disregard the possibility of hypoglycemic episodes as a result of the interplay between drug treatment, viral pathogenesis and typical metabolic disturbances of diabetes. Patient tailored therapeutic strategies and optimal glucose control goals should be formulated based on disease severity, presence of

comorbidities and diabetes-related complications, age and other factors. A multidisciplinary team approach, including infectologists, endocrinologists, pulmonologists, psychologists, nutritionists and exercise rehabilitation specialists may be necessary during the prolonged hospitalization periods and recovery. Special attention should be paid to those with diabetic nephropathy, or diabetes-related heart complications, since they are also at higher risk for severe COVID-19 and death [7,19]. Finally, increased vigilance and testing in outpatient diabetes clinics for COVID-19, as well as lower thresholds for hospitalization of these patients may have a positive impact on their outcomes.

5. Conclusions

COVID-19 has rapidly spread since its initial identification in Wuhan and has shown a broad spectrum of severity. Early isolation, early diagnosis, and early management might collectively contribute to a better control of the disease and outcome. Diabetes and other comorbidities are significant predictors of morbidity and mortality in patients with COVID-19. Future research is urgently needed to provide a better understanding regarding potential differences in genetic predispositions across populations, underlying pathophysiological mechanisms of the association between COVID-19 and diabetes, and its clinical management.

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A.H., N.C.d.V.M. and B.B. conceptualized and wrote the paper; A.H. and N.C.d.V.M. revised the text; and all approved the final manuscript.

Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

Declaration of Competing Interest

None.

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