

SECONDARY DISEASES OF INFECTIOUS AND NON-INFECTIOUS ORIGIN IN PATIENTS DIAGNOSED WITH COVID-19

DOI: <https://doi.org/10.24115/S2446-622020217Extra-A780p.76-85>

Vitaly Viktorovich Goncharovⁱ 

Mikhail Andreevich Ugrovatovⁱⁱ 

Harun Achmadⁱⁱⁱ 

Nelly Al Audah^{iv} 

Mariya Andreevna Kishkina^v 

ABSTRACT

The article considers the features of the occurrence and course of secondary diseases of infectious and non-infectious genesis in patients with a diagnosis of COVID-19, and also examines individual clinical cases described in the literature. The author concludes that the results showed that major respiratory diseases, in particular COPD (chronical obstructive pulmonary disease) and smoking, are associated with severe COVID-19 outcomes. The results of this study can help policy makers, doctors and healthcare professionals in the front line to make evidence-based decisions and reduce the mortality and morbidity of this 21st century pandemic. Understanding the proportion of COVID-19 patients with acute respiratory bacterial co-infection and pathogens is critical for the treatment of COVID-19 patients and helps ensure responsible use of antibiotics and minimize the negative effects of overuse. In addition, this knowledge may have a significant impact on clarifying recommendations for empirical antibiotic therapy for patients with COVID-19.

Keywords: COVID-19. Secondary diseases. Infectious and non-infectious genesis. Disease outcomes.

DOENÇAS SECUNDÁRIAS DE ORIGEM INFECCIOSA E NÃO INFECCIOSA EM PACIENTES DIAGNÓSTICOS COM COVID-19

ENFERMEDADES SECUNDARIAS DE ORIGEN INFECCIOSO Y NO INFECCIOSO EN PACIENTES DIAGNOSTICADOS CON COVID-19

RESUMO

O artigo considera as características da ocorrência e evolução das doenças secundárias de gênese infecciosa e não infecciosa em pacientes com diagnóstico de COVID-19, e também examina casos clínicos individuais descritos na literatura. O autor conclui que os resultados mostraram que as principais doenças respiratórias, em particular a DPOC (doença pulmonar obstrutiva crônica) e o tabagismo, estão associadas a desfechos COVID-19 graves. Os resultados deste estudo podem ajudar os formuladores de políticas, médicos e profissionais de saúde na linha de frente a tomar decisões baseadas em evidências e reduzir a mortalidade e morbidade desta pandemia do século XXI. Compreender a proporção de pacientes com COVID-19 com coinfeção bacteriana respiratória aguda e patógenos é fundamental para o tratamento de pacientes com COVID-19 e ajuda a garantir o uso responsável de antibióticos e minimizar os efeitos negativos do uso excessivo. Além disso, esse conhecimento pode ter um impacto significativo no esclarecimento das recomendações para antibioticoterapia empírica para pacientes com COVID-19.

Palavras-chave: COVID-19. Doenças secundárias. Gênese infecciosa e não infecciosa. Resultados da doença.

RESUMEN

El artículo considera las características de la aparición y el curso de enfermedades secundarias de génesis infecciosa y no infecciosa en pacientes con un diagnóstico de COVID-19, y también examina los casos clínicos individuales descritos en la literatura. El autor concluye que los resultados mostraron que las principales enfermedades respiratorias, en particular la EPOC (enfermedad pulmonar obstructiva crónica) y el tabaquismo, están asociadas con resultados graves de COVID-19. Los resultados de este estudio pueden ayudar a los responsables políticos, médicos y profesionales de la salud en la primera línea a tomar decisiones basadas en evidencia y reducir la mortalidad y morbilidad de esta pandemia del siglo XXI. Comprender la proporción de pacientes con COVID-19 con coinfección bacteriana respiratoria aguda y patógenos es fundamental para el tratamiento de los pacientes con COVID-19 y ayuda a garantizar el uso responsable de antibióticos y minimizar los efectos negativos del uso excesivo. Además, este conocimiento puede tener un impacto significativo en aclarar las recomendaciones para la terapia antibiótica empírica para pacientes con COVID-19.

Palabras-clave: COVID-19. Enfermedades secundarias. Génesis infecciosa y no infecciosa. Resultados de la enfermedad.

INTRODUCTION

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as of September 27, 2020, affected more than 32 million patients worldwide (Chen et al., 2020). The clinical manifestations of this condition (coronavirus disease 2019, COVID-19) range from asymptomatic infection to severe viral pneumonia requiring treatment in the intensive care unit (ICU) (KLOK et al., 2020).

Bacterial infections are an important problem in this regard. Bacterial co-pathogens are usually detected in viral infections of the respiratory tract, such as influenza, and are an important cause of morbidity and mortality, which requires timely diagnosis and antibacterial therapy (HELMs et al., 2020). Although bacterial co-infection varies greatly in patients with severe influenza, it is reported to reach 20-30% (DOLHNKOFF et al., 2020) and is associated with greater disease severity, greater use of health resources, and an increased risk of infection. death (REDDY et al., 2020). The prevalence, frequency, and characteristics of bacterial infection in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are poorly understood and are considered an important knowledge gap (PORFIDIA et al., 2020).

The impact of the pandemic goes beyond patients with COVID-19. This affected patients with non-COVID-related diseases such as cancer (ROSENBAUM, 2020), developmental and epileptic encephalopathies (ALEDÓ-SERRANO et al., 2020) and ST-segment elevation myocardial infarction (TAM et al., 2020). A recent systematic review reported that individual cases of Guillain-Barré syndrome (GBS) occurred secondary to COVID-19 infection. GBS is defined as a rare, but potentially fatal, immune-mediated disease of the peripheral nerves and nerve roots that is usually caused by infections. Thus, the incidence of GBS may increase during outbreaks of infectious diseases.

Despite current knowledge, there is no definitive cure for COVID-19, and many people die every day around the world. A deep and comprehensive view of the interaction between the virus and the immune system helps us develop an effective therapeutic strategy. However, it is quite important to prevent the development of secondary diseases of infectious and non-infectious origin in patients who have had COVID-19, as this can have sharply negative consequences for the health of the nation.

The aim of the work is to consider the features of the occurrence and course of secondary diseases of infectious and non-infectious Genesis in patients with a diagnosis of COVID-19. Materials and methods. The study was based on materials from the clinical practice of specialists of various medical specialties, and various articles were also used within the designated research topic.

RESULTS

Current research shows that the prevalence of major respiratory diseases was an important predictor of severe COVID-19 outcomes. In particular, significant respiratory diseases are reported in patients with severe COVID-19 compared to non-severe (OR 2.46, 95% CI: 1.76-3.44) (SU et al., 2020). Respiratory diseases were reported using a General variable that could potentially group different conditions or relate specifically to COPD. There was no information on other respiratory diseases, except for one study that reported the prevalence of COPD, asthma, and secondary pulmonary tuberculosis (ZHENG et al., 2020). Consequently, questions arise about the causes leading to a lack of information about the prevalence of respiratory diseases other than COPD and the severity of COVID-19 in the literature.

The authors determined that COPD is often misclassified due to insufficient use of confirmatory spirometry and because a medical professional performs a diagnostic assessment (MAGRO et al., 2020). However, it is also possible that other respiratory diseases were underdiagnosed or not properly documented in databases, which is unlikely since this information was not available in most studies, including the report of the Centers for Disease Control and Prevention (CDC) in the United States (BANGALORE et al., 2020). Another possibility may be that the prevalence of other respiratory diseases may not be associated with severe COVID-19 outcomes due to their specific immune response and / or pharmacological treatment (MAFHAM et al., 2020). For example, asthma treatment usually involves the use of bronchodilators and inhaled corticosteroids, which have been shown to inhibit coronavirus replication and cytokine production in in vitro models (BRAITEH et al., 2020). In General, the relationship of COVID-19 severity to specific respiratory diseases other than COPD (e.g., asthma, pulmonary tuberculosis, pulmonary fibrosis, etc.) and their causal mechanisms require further investigation. Severe COVID-19 outcomes have been largely associated with smoking now and in the past. It is suggested that smoking may play a role in modulating angiotensin-converting enzyme 2 (ACE2) (kapoor, 2020), which is reported to be a host receptor for the virus responsible for COVID-19 (DRIGGIN et al., 2020). A dose-dependent increase in ACE2 expression depending on smoke exposure was found in rodent and human lungs (LI et al., 2020).

A recent publication suggested that the predisposition of smokers to severe SARS-CoV-2 infections may be at least partially explained by the response of ACE2 expression to inflammatory signaling, which may be enhanced by viral infections (TROYER et al., 2020). In addition, increased ACE2 expression was observed in COPD, a respiratory disease closely associated with smoking in previous time and severe COVID-19 outcomes (LI et al., 2020). However, more research will be needed to determine the linkage of smoking, COPD, and ACE2 levels with the clinical course of COVID-19.

The high risk of the disease in question often leads to the death of patients. According to research, the dead infected with SARS-CoV-2 were mostly men over 70 years of age, diabetics, and hypertensive patients. In addition, comorbidities have been reported in infected individuals, including kidney disease, heart failure, and chronic obstructive pulmonary disease (COPD) (DESAI & LAW, 2011). Patients over 70 years of age compared to people under 50 years of age showed that the risk of severe COVID-19 is 5-10 times higher (SIDDIQI & MEHRA, 2020). Men with diabetes, hypertension, COPD, or cardiovascular disease experienced a twofold increase in severe disease or mortality. High body mass index (BMI) and obesity are also attributed to severe / fatal disease (ZANGRILLO et al., 2020).

The severity of COVID-19 was also associated with the distribution of adipose tissue in the abdominal cavity, which indicates the potential pathogenic involvement of visceral obesity in the acute form of the disease (PAGNESI et al., 2020). However, the data do not support an increased risk of serious illness or death due to tobacco smoking (BLOT et al., 2012). Innate immune cells, along with physical barriers, are an early innate immune response to viral lung infections. Innate immune cells include macrophages, DCs, neutrophils, and parenchymal cells such as fibroblasts and epithelial cells. Some innate immune cell receptors, called pattern recognition receptors, are responsible for detecting antigens associated with the virus. Toll-like receptors (TLR) that recognize pathogen-associated molecular patterns (PAMP), RIG-I-like receptors that recognize nucleic acids, lectin-like C-type receptors (CLR), and NOD-like receptors (NLR) are pattern recognition receptors (PRR).) is responsible for identifying viral antigens (FINE & GRAY, 1999).

A sufficiently intense innate response is required to ease the burden of the battle for adaptive immunity. The more effective cleaning measures in the early stages of the disease, the less harmful inflammatory consequences. Stimulation of innate immune cells leads to the secretion of inflammatory mediators, such as IL-6 and type I / III interferons (IFN), which together with the complement system play a role against viral progression in the early stages (KIM, 2007). However, viruses develop mechanisms to evade innate immunity. For example, viruses can intelligently evade the complement system by removing antibody-antigen complexes from the cell surface, reducing Fc receptor expression, or mimicking complement regulatory components (ZHOU et al., 2020).

The interaction of the virus with innate immunity has a decisive effect on the adaptive immune response against the virus and thus on virus elimination and clinical outcome. Accordingly, due to the complex interactions between the virus and innate immunity, the immune system can sometimes delay recovery, progress the disease, or even cause death. As a lever of innate immunity, the complement system begins to act in the acute phase of the disease. Various strategies developed in viruses to bypass the complement system have shown that complement proteins play an important role in antiviral protection (HE et al., 2020).

The supplement plays a double-edged sword role in innate immunity against pathogens. On the one hand, anaphylatoxins such as C3a and C5a can activate immune cells and thereby induce the release of various pro-inflammatory cytokines. Activated complement fragments, such as the membrane attack complex (MAC), C3b and C5b, induce the synthesis of arachidonic acid metabolites, including prostaglandins and leukotrienes, promoting inflammatory processes and directing innate immunity against the virus. On the other hand, complement-mediated activation of innate immunity must be regulated, because uncontrolled complement activation exacerbates inflammation, promotes disseminated intravascular coagulation (DIC), and ultimately leads to multiple organ failure and death (GOYAL et al., 2020).

Secondary diseases are particularly dangerous in COVID-19. For example, a case was reported of a patient who developed extensive symptomatic hemorrhagic pericardial effusion that caused cardiac tamponade. There were no initial signs of cardiac damage or myocardial damage, as indicated by the absence of cTnI elevation or wall movement abnormalities on the TTE. In fact, her symptoms were relatively mild before developing pericardial effusion. Viral infections are a common cause of pericarditis and usually have a benign course (GOYAL et al., 2020). Hemorrhagic effusion in the pericardium is less often associated with viral infections, but Coxsackie virus has been reported (CHEN et al., 2020). It is assumed that viruses cause pericardial inflammation through direct cytotoxic effects or through immuno-mediated mechanisms (HUANG et al., 2020).

The literature has reported that COVID-19 causes an excessive systemic inflammatory response in some patients; however, the details of this response are not fully understood (CHEN et al., 2020). It is likely that COVID-19, like other viral infections, causes an inflammatory response leading to pericarditis and subsequent effusion; however, the exact mechanism is unclear. Hemorrhagic effusions have also been reported in other inflammatory conditions, such as Dressler syndrome, which is believed to be the result of deposition of immune complexes and the subsequent inflammatory cascade after myocardial infarction (DONG et al., 2020).

The results of the publication study showed that cardiovascular consequences, including acute heart injury, arrhythmia, coronary heart disease, hypertension, and cardiovascular disease, were significantly associated with the admission of a COVID-19 patient to the intensive care unit. Comparison of the combined OR score for cardiovascular diseases showed that the probability of hospitalization in the ICU was significantly higher for acute heart injury and arrhythmia than for hypertension, but there was no significant difference between other cardiovascular consequences (CHEN et al., 2020).

Studies have shown that mortality in patients with acute heart injury was significantly higher than in patients with coronary heart disease, arrhythmia, and hypertension. Comparison of the estimated frequency of various cardiovascular complications, including acute heart injury, arrhythmia, cardiomyopathy, coronary heart disease, palpitation, hypertension, Previously, cardiovascular complications have been reported for previous respiratory infections of similar etiology, and their condition affects the severity of the disease (LIU et al., 2020); so even hospitalization for pneumonia is associated with a long-term and short-term risk of cardiovascular disease (ZHOU et al., 2020).

Viral infections cause an imbalance between cardiac supply and demand and increase systemic inflammation. Therefore, patients with pre-existing CVD have a higher risk of acute heart conditions, thrombosis, infection, and the development of severe conditions during infection (MACINTYRE et al., 2018). The thrombotic complications of COVID-19 infection are well known. Although there have been several reports of myocardial damage secondary to SARS-CoV-2 infection, this is the first report of coronary artery occlusion confirmed by catheter angiography and cardiac imaging. In one study, during the COVID-19 pandemic, the number of hospital admissions for acute coronary syndromes decreased by about 40%, which probably reflects the preference of patients to stay at home when symptoms appear, given the risk of transmission of the virus in medical institutions. Other studies have confirmed this decrease in the number of hospital admissions to ACS, raising concerns that a large number of patients with the consequences of untreated acute coronary syndrome, such as heart failure, may come out of the pandemic.

The link between COVID-19 infection and cardiovascular disease is well known. Studies have shown that patients infected with SARS-CoV-2 with pre-existing cardiovascular disease have an increased risk of severe illness and death. One study demonstrated an 8% risk of acute heart injury in patients with COVID-19 and a 13-fold higher risk in critically ill patients. Notably, almost all of these studies used biomarkers and / or ECGs to diagnose acute myocardial injury. Radiology can play a key role in differentiating these formations, which is confirmed by the results of MRI of the patient's heart. Given the different treatment strategies for myocarditis compared to coronary thrombosis, the results of catheter angiography and cardiac imaging may serve as a critical moment in the treatment of patients with heart symptoms in the context of COVID-19 infection.

A PKA infarction in one of the patients described in the study led to a cascade of events, starting with wall movement abnormalities that were visualized on both a bedside echocardiogram and an MRI of the heart that predisposed to the formation of a left ventricular clot. The absence of this clot in a subsequent echo study after an ischemic infarction suggests that it may have embolized into the brain's vascular network. Given the state of hypercoagulation caused by COVID-19 and immobilization in the critical care unit (CCU), an alternative possibility is that the brain infarction is a separate blood clot. Indeed, many critically ill COVID-19 patients end up dying from multiple organ failure, which is thought to be partially related to multiple thrombotic complications (MEMISH et al., 2020). The long-term complications of COVID-19 are becoming increasingly apparent. Persistent interstitial abnormalities and scarring of the lung parenchyma leading to pulmonary fibrosis have become an important and worrisome complication that occurs in many patients. Reports of long-term neurological consequences also raise questions about the extent of brain involvement in acute infection and whether symptoms can be expected to disappear completely.

In addition to direct infection with the virus, thrombosis that occurs against the background of acute COVID-19 can also have long-term consequences. Prior to this episode, our patient had no cardiovascular disease. Although his ejection fraction (EF) improved from about 15% to 35% by the end of his hospitalization, the heart attack resulted in long-term suboptimal heart function. Similarly, a large infarction of right brain - in middle

cerebral artery (MCA) in this patient led to long-term disability. Neurological damage from COVID-19 is not uncommon and may be the result of the virus itself or a brain infarction (LI et al., 2020). Numerous long-term complications of long-term intensive care have been described, probably directly applicable to critically ill patients with COVID-19, given the long duration of stay in the intensive care unit.

Given the risk of thrombotic complications in patients with COVID-19, clinical guidelines have been issued recommending the use of anticoagulants in hospitalized patients with COVID-19 with continued treatment for high-risk patients. From a clinical point of view, the level of suspicion of thrombosis in patients with SARS-CoV-2 infection should be increased and appropriate imaging should be prescribed to confirm that therapeutic anticoagulation can be initiated to prevent long-term complications of thrombosis.

Practice shows that in conditions of high transmission of COVID-19 among the population, one should be afraid that the infection is the cause of non-specific symptoms or symptoms that can be attributed to a different etiology. The initial treatment of individual patients, for example, in the emergency department could be associated with asthma, but it is possible that such manifestations have an early infection of COVID-19. Prolonged infection without follow-up can lead to acute coronary syndrome, which eventually leads to heart failure, ventricular thrombosis, and brain infarction. In addition, the patient may have infected hundreds of people with COVID-19 between visits to the emergency Department. Clinicians should be vigilant when recognizing COVID-19 infection, as well as its complications.

COVID-19 also leads to complications in children. All along the path of the Covid-19 pandemic; the number of affected children does not exceed 2% according to a number of publications (HUANG et al., 2020). throughout the pandemic, the authors reported the appearance of multi-organ inflammatory syndrome (MIS-C: Multisystem inflammatory syndrome in children), which is similar to Kawasaki disease. The causal relationship with Covid-19 is well established, suggesting an intense immune response that occurs late due to a primary viral infection that went unnoticed. The main symptoms observed are high fever, vasoplegic shock, neurological disorders, and almost permanent digestive disorders. but so far, none of the authors have reported a case of intestinal ischemia in children.

A case was reported where an Algerian girl underwent emergency surgery for pseudo-appendicular syndrome associated with Multisystem disorder (MIS-C) in a child with weakened immune system (YANGA et al., 2020). The number of children affected by Covid 19 is about 2% of the General population (2% in the UK, 1.7% in the US, 1% in the Netherlands (TAI et al., 2019).

Symptoms are most often benign (45.5%), the average form is about 41.5%, severe - 4.4%. Critical form 0.9%, deaths are rare (3 cases), according to a series published by Xiaojian Cui 2596 children (KEICHO et al., 2009). Digestive disorders associated with the direct involvement of the virus are rare: diarrhea 6.6%, vomiting 5.8% (LI et al., 2020). Throughout this pandemic, W. G. Jones (USA) first reported Multisystem inflammatory syndrome (MIS-C) on April 7, 2020: a six - month-old baby with Kawasaki disease associated with a positive Covid-19 test (KATZE et al., 2002). Since then, other cases related to covid-19 and suggesting a post-viral immune response have been reported.

May 6, 2020: Riphagen (UK) reported a series of 8 cases of MIS-C.

May 13, 2020 Verdoni (Italy) published a series of 10 cases (PCR +: 20%, serological IgG +: 80%). may

14, 2020 Tubiana (France): 17 cases (PCR +: 41% and serological IgG +: 88%)

And on may 17, 2020, the new York state Department of health issues a warning identifying more than 100 cases of MIS-C related to Covid 19 (BERNET et al., 2003). Clinical data were most often expressed with fever for more than 4 days with persistent vasoplegic shock. 55% of the patients required vasoactive drugs, digestive symptoms come to the fore (83%); we also noticed heart damage on echocardiography (69%), neurological signs: headaches, irritability, confusion and irritation of the meningeal vessels (61%), skin lesions increased to 69%, chest imaging was seen within 44%

Recently, 5 cases of pneumomediastinum were reported after intubation in COVID-19. The development of pneumomediastinum from the moment of tracheal intubation ranged from 4 hours to 14 days. Four patients also had subcutaneous emphysema. Our patient (Wali et al.) also developed subcutaneous emphysema, pneumopericardium, and pneumomediastinum. An increased risk of alveolar damage, tracheobronchial damage, and higher ventilation pressure were suggested as possible mechanisms for the development of pneumomediastinum. Three of the five patients reported to have survived. In contrast to the case of Wali et al., one patient developed spontaneous pneumomediastinum and pneumopericardium without any direct trauma

such as intubation. A possible explanation for spontaneous pneumomediastinum can be explained by the Macklin effect.

This phenomenon is defined as the tracking of alveolar air from ruptured alveoli along the peribronchial vasculature towards the mediastinum and pericardium. (WANG et al.,) One patient was reported who simultaneously developed pulmonary pathologies with spontaneous pneumothorax, pneumomediastinum, and subcutaneous emphysema. The current body of evidence in regions with a high COVID-19 burden worldwide suggests that superinfections are common, especially in severe cases. In a study conducted in Wuhan, out of 41 patients, secondary infections were reported in 31% of patients in the intensive care unit and in 10% of patients overall. In another study conducted in Wuhan, of 68 patients who died, 11/68 (16%) were found to have secondary infections, although further details were not provided (BETTELLI et al., 2006). In this study, we found that out of 151 patients with secondary infections, 56 (37%) were intensive care patients, and among these patients there was a hospital mortality rate of 33%.

Like our results, most pathogens reported in patients with COVID-19 are hospital-acquired multidrug-resistant (MDR) microorganisms. In our center, MDR was detected in 60% of isolates, and the genes of antimicrobial resistance (AMR) were also found in bacteria, co-infectious patients with COVID-19. Published ICMR data indicate a high prevalence of AMR in Indian hospitals in the pre-COVID period. High antimicrobial pressure in intensive care units to treat COVID-19 patients with empirical antimicrobial drugs will further exacerbate the problem of AMR. This is especially true for COVID-19 centers that do not have adequate microbiological support for cultivation, or the culture of cultivation does not exist (due to fear of taking samples or lack of policies / resources).

In contrast to normal circumstances, in patients with COVID-19, various invasive methods that are otherwise used to diagnose secondary infections are limited as part of infection control measures. Thus, doctors often resort to empirical broad-spectrum antimicrobial therapy. Taking into account, that empirical prophylactic antibiotics may instead select MDR pathogens, if clinicians lower their threshold for culture data and prefer targeted antibiotic therapy over empirical prevention, this will allow for later reduction of escalation or re-targeting of treatment. This will also lead to fewer secondary infections and favorable outcomes in patients with COVID-19.

Limited evidence suggests that nosocomial infections are associated with increased COVID-19 severity, prolonged ICU stay, and a higher risk of death (Hunter & Jones, 2015). For example, in one study, nosocomial mortality was observed in 50/151 (33%) patients with COVID-19 with secondary infections. It was found that it is statistically significant that in 24% of the total number of hospital deaths, the cause was secondary infection. Secondary blood diseases left the majority of secondary infections: 58 out of 731 patients (7.9%) had at least one case. A high incidence of such diseases due to coagulase-negative staphylococci and a significant proportion of patients with multiple isolates have been documented (HOTEZ & BOTTAZZI, 2020). This finding may reflect the high burden of catheter-associated infections. However, there were no data on the presence of intravascular catheters.

Several factors may have contributed to a higher incidence of secondary infectious blood diseases due to coagulase-negative staphylococci. First, being at the epicenter of the COVID-19 pandemic in our country and given the unprecedented strain on our health system, critically ill patients with multiple devices were treated outside the intensive care unit, which may have led to an increase in diagnoses related to blood diseases.

Second, the conditions of the pandemic may have reduced compliance with strict aseptic procedures, especially in critically ill patients outside the intensive care unit or in crowded or makeshift intensive care units. Moreover, adequate use of personal protective equipment can be problematic and could potentially lead to a reduction in compliance with aseptic methods when handling intravascular devices.

Reviews were also conducted on concomitant bacterial infections in patients hospitalized with COVID-19; 24 studies were included. Co-infection was reported in 3.5% (95% CI: 0.4–6.7%) of patients, and secondary infection was reported in 14.3% (95% CI: 9.6–18.9%) of patients with COVID-19. Overall, the reported bacterial infection was 6.9% (95% CI 4.3–9.5%), but varied slightly depending on the patient population: from 5.9% in hospitalized patients to 8.1% in critically ill patients. Despite the overall low level of bacterial infections, more than 70% of patients received antibiotics, most of which were broad-spectrum agents such as fluoroquinolones and third-generation cephalosporins. A total of 30 studies were conducted evaluating co-infections among patients infected with COVID-19. Similarly, the authors reported that 7% of patients had bacterial co-infection with a high degree of heterogeneity ($I^2 = 92.2\%$) and a higher prevalence in intensive care units compared to mixed inpatient facilities (Frieman et al., 2008).

DISCUSSION

The results showed that major respiratory diseases, particularly COPD and Smoking, increase the likelihood of severe COVID-19 outcomes. This is an important finding, given the high prevalence of COPD and Smoking worldwide, as well as the rapid spread of SARS-CoV-2. Research results can support the development of preventive interventions, including training of patients and healthcare professionals, and contribute to improving the assessment and management of patient risk factors in clinical practice, leading to mitigation of severe outcomes in patients with COVID-19 infection (HUANG et al.).

From a public health perspective, these results may have implications for policy development and potential funding for respiratory diseases such as COPD. Moreover, Smoking cessation programs and efforts should be expanded, given the link between severe COVID-19 outcomes and Smoking. Future studies should evaluate the Association of severe COVID-19 outcomes with the prevalence of respiratory diseases other than COPD, and examine the potential impact of their immune responses and pharmacological treatment. In addition, the Association of severe COVID-19 outcomes with all levels of Smoking status and causal mechanisms should be studied.

There are also many factors to consider. First, there is limited information about respiratory diseases and Smoking presented in the identified studies, which does not allow us to draw further conclusions about the specific role of each risk factor in the development of severe COVID-19 outcomes. Evidence suggests that there is a close relationship between COPD, Smoking, and ACE2 modulation, which may increase the risk of severe COVID-19 outcomes, but more research is needed to clarify this relationship. Second, the studies mentioned in this review were mostly conducted in China (95%). It is possible that factors such as the prevalence of respiratory diseases and their treatment, among other things, may be context-specific. Therefore, the results of this study should be treated with caution and re-evaluated as new literature from other countries becomes available (BECKER, 2020; Klok et al., 2020; ACHMAD et al., 2020).

It should also be said that patients with rare diseases experienced special difficulties when being admitted to hospitals. Access to health care has become more difficult due to the perceived risk of COVID infection by patients and their caregivers, and the allocation of health resources to reduce the number of non-emergency services. The impact of COVID-19 on infected patients and the high rate of infection worldwide has caused many to worry about infection, especially those who are more vulnerable with existing comorbidities (KLOK et al., 2020; ACHMAD et al., 2020; ACHMAD et al., 2020; ACHMAD ET al., 2018).

CONCLUSIONS

The results showed that major respiratory diseases, particularly COPD and Smoking, are associated with severe COVID-19 outcomes. These results contribute to a better understanding of risk factors for patients with severe COVID-19, which are important to support the development of preventive interventions and can help improve the assessment and management of risk factors for patients in clinical practice. Future studies should evaluate the Association of severe COVID-19 outcomes with the prevalence of other major respiratory diseases other than COPD, as well as explore the potential impact of their immune responses and pharmacological treatment. In addition, the Association of severe COVID-19 with all Smoking levels and causal mechanisms should be the subject of future research.

Cardiovascular diseases play an important role in the severity of disease and mortality in patients with COVID-19. Hypertension, acute heart injury, and coronary heart disease in a patient with COVID-19 require careful monitoring and treatment in the case of acute conditions. Other cardiovascular disorders, including arrhythmia and heart failure, must also be considered, as they can be fatal. Therefore, in these patients, careful consideration and treatment of cardiovascular diseases is necessary. The results of this study can help policy makers, doctors and healthcare professionals in the front line to make evidence-based decisions and reduce the mortality and morbidity of this 21st century pandemic.

Understanding the proportion of COVID-19 patients with acute respiratory bacterial co-infection and pathogens is critical for the treatment of COVID-19 patients and helps ensure responsible use of antibiotics and minimize the negative effects of overuse. In addition, this knowledge may have a significant impact on clarifying recommendations for empirical antibiotic therapy for patients with COVID-19.

REFERENCES

- ACHMAD, H. et al. A Review of Bandotan Leaf Extract (*Ageratum conyzoides* L.) in Inhibition Test to the Growth of Bacteria (*Porphyromonas gingivalis*) Case of Periodontitis Disease. *Systematic Reviews in Pharmacy*, 2020; 11(4): 390-395. Available at: <https://www.sysrevpharm.org/articles/a-review-of-bandotan-leaf-extract-ageratum-conyzoides-l-in-inhibition-test-to-the-growth-of-bacteria-porphyromonas-gingi.pdf>. Access: Oct.22, 2020.
- ACHMAD, H. et al. Analysis of disease risk factors of early childhood caries (Ecc) On Pre-School Children Psychosocial Project Review. *Asian Journal. of Microbiol. Biotech. Env Sc. Global Science Publications*, 2020, p. 18-25, Vol. 20, Oct. Suppl Issue. ISSN-0972-3005.
- ACHMAD, H. et al. Impact of COVID-19 in Pediatric Dentistry: A Literature Review. *International Journal of Pharmaceutical Research*, January-June, 2020. Supplementary Issue 1. p. 830-940.
- ACHMAD, H. et al. Teledentistry as a solution in dentistry during the Covid-19 pandemic period: a systematic review. *Journal of Pharmaceutical Research*, July-December, 2020. Supplementary Issue 2. 272-278.
- BANGALORE, S. et al. ST-segment elevation in patients with Covid-19 - a case series *N. Engl J Med*, 382 (25), 2020, p. 2478-2480.
- BECKER, R.C. COVID-19 update: covid-19-associated coagulopathy *J. Thromb. Thrombolysis*, 50, 2020, p. 54-67.
- BERNET, J.; MULLICK, J.; SINGH, A.K.; SAHU, A. Viral mimicry of the complement system *J. Biosci.*, 28 (3), 2003, p. 249-264.
- BETTELLI, E. al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells *Nature*, 441 (7090), 2006, p. 235-238.
- BLOT, S.I. et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients *Am J Respir Crit Care Med*, 186. 2012, p. 56-64.
- BRAITEH, N. et al. Decrease in acute coronary syndrome presentations during the COVID-19 pandemic in upstate New York *Am Heart J*, 226, 2020, p. 147-151
- CHEN, N. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study *Lancet*, 395 (10223), 2020, p. 507-513
- DESAI, S.V. et al. Long-term complications of critical care. *Crit Care Med*, 39 (2), 2011, p. 371-379.
- DOLHNIKOFF, M. et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost*, 18 (6), 2020, p. 1517-1519.
- DONG, X. et al. Eleven faces of coronavirus disease 2019. *Allergy* [Internet], 75 (7), 2020, p. 1699-1709.
- DRIGGIN, E. et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol*, 75 (18), 2020, p. 2352-2371.
- FINE, J.P.; GRAY R.J. A proportional hazards model for the subdistribution of a competing risk. *J Am Statist Assoc*, 94, 1999, p. 496-509.
- FRIEMAN, M. et al. SARS coronavirus and innate immunity. *Virus Res.*, 133 (1), 2008, p. 101-112.
- GOYAL, P. et al. Clinical characteristics of covid-19 in New York city. *N Engl J Med* [Internet], 382 (24), 2020, p. 2372-2374.
- HE, Y. et al. Nosocomial infection among patients with COVID-19: a retrospective data analysis of 918 cases from a single center in Wuhan. *China Infect Control Hosp Epidemiol* [Internet], 2020, p. 1-2.
- HELMS, J. et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study *Intensive. Care Med*, 46 (6), 2020, p. 1089-1098.

- HOTEZ, P.J. et al. The potential role of Th17 immune responses in coronavirus immunopathology and vaccine-induced immune enhancement. *Microbes Infect*, 22 (4–5), 2020, p. 165-167.
- HUANG, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* [Internet], 395 (10223), 2020, p. 497-506.
- HUANG, K.J. et al. An interferon-gamma-related cytokine storm in SARS patients. *Med Virol*, 2005 Feb;75(2):185-94.
- HUANG, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395 (10223), 2020, p. 497-506.
- HUNTER, C.A.; JONES, S.A. IL-6 as a keystone cytokine in health and disease. *Nat. Immunol.*, 16 (5), 2015, p. 448-457.
- KAPOOR, A.; YADAV, R. Will the hidden specter of acute coronary syndrome (ACS) and ST-segment elevation myocardial infarction (STEMI) emerge from the avalanche of COVID-19? *Indian Heart J*, 72 (3), 2020, p. 192-193.
- KEICHO, N. et al. Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. *Hum. Immunol.*, 70 (7), 2009, p. 527-531.
- KIM, H.T. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res*, 13, 2007, p. 559-565.
- KLOK, F.A. et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*, 191, 2020, p. 145-147.
- KLOK, F. et al. Incidence of thrombotic complications in critically ill ICU patients with COVID19. *Thromb. Res.*, 191, 2020, p. 145-147.
- LI, B. et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19. In: *China Clin Res Cardiol*, 109 (5), 2020, p. 531-538.
- LI, H. et al. The profile of peripheral blood lymphocyte subsets and serum cytokines in children with 2019 novel coronavirus pneumonia. *J Infect* [Internet], 81 (1), 2020, p. 115-120.
- LI, Z. et al. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. *Front Med*, 2020, p. 1-9.
- LI, G. et al. Coronavirus infections and immune responses. *J. Med. Virol.*, 92 (4), 2020, p. 424-432.
- LIU, Y. et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*, 63, 2020, p. 364-374.
- M.G. Katze, Y. He, M. Gale Jr. Viruses and interferon: a fight for supremacy. *Nat. Rev. Immunol*, 2 (9), 2002, p. 675-687.
- MACINTYRE, C.R. et al. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza A(H1N1)pdm09. *BMC Infect Dis*, 18, 2018, p. 637.
- MAFHAM, M.M. et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet*, 396 (10248), 2020, p. 381-389.
- MAGRO, C. et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*, 220, 2020, p. 1-13.
- MEMISH, Z.A. et al. Middle East respiratory syndrome. *Lancet*, 395, 2020, p. 1063-1077.
- PAGNESI, M. et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19 *Heart*, 106, 2020, p. 1324-1331.

PORFIDIA, A. et al. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thromb Res*, 196, 2020, p. 67-74.

REDDY, S.T. et al. Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. *Case Rep Neurol*, 12 (2), 2020, p. 199-209.

SIDDIQI, H.K.; MEHRA, M.R. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*, 39, 2020, p. 405-407.

SU, H. et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in: *China Kidney Int*, 98 (1), 2020, p. 219-227.

TAI, W. et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cell. Mol. Immunol.*, 17 (6), 2020, p. 613-620.

TROYER, E.A. et al. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*, 87, 2020, p. 34-39.

YANGA, J. et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. *Int. J. Infect. Dis.*, 94, 2020, p. 91-95.

ZANGRILLO, A. et al. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. *Crit Care Resusc*, 22, 2020, p. 200-211.

ZHENG, Y. et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*, 17 (5), 2020, p. 259-260.

ZHOU, F. al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395, 2020, p. 1054-1062.

ZHOU, F. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 395, 2020, p. 1054-1062.

ⁱKuban State Agrarian University Named after I.T. Trubilin, 350044, Krasnodar, Kalinina street, house 13, Russian Federation. Email: niipgergo2009@mail.ru. ORCID: <https://orcid.org/0000-0003-3029-4727>.

ⁱⁱFederal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University). Email: ugrovatovui@mail.ru. ORCID: <https://orcid.org/0000-0002-8593-9580>.

ⁱⁱⁱDepartment of Pediatric Dentistry, Faculty of Dentistry, Hasanuddin University, Indonesia. Email: h45iop@mail.ru. ORCID: <https://orcid.org/0000-0002-4339-5431>.

^{iv}Department of Microbiology and Parasitology, Faculty of Medicine, Lambung Mangkurat University. Banjarmasin, South Kalimantan. Indonesia. Email: 75694ereyandex.ru. ORCID: <https://orcid.org/0000-0003-1707-9715>.

^vFederal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University). Email: km23c@yandex.ru. ORCID: <https://orcid.org/0000-0001-7505-8627>.