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Risk Factors Associated with the Progression and Proliferation of Novel Covid-19: A Systematic Review

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Abstract: *Since December 2019, infectious pneumonia broke out in Wuhan, Hubei province. The pathogen was designated as SARS-CoV-2 by the International Committee on Taxonomy of Viruses, and this pneumonia was named as Coronavirus Disease2019 (COVID-19) by World Health Organization (WHO). Nowadays, there were about 34,804,348 cases of COVID-19 confirmed worldwide, with a total of 1,030,738 deaths in 216 countries/territories according to WHO report as of October 4th, 2020. The rapidly increasing of patients, especially the critical or mortal patients, brought a big challenge to the public health. Several factors are responsible for the severity and mortality of COVID-19 disease. From different studies, it had been found that patients with comorbidities such as hypertension, diabetes mellitus, acute respiratory distress syndrome (ARDS), cardiovascular disease, cancer, COPD, asthma, renal disease, kidney disease, liver disease, hepatic disease, pneumonia, obesity, and also for the history of smoking were responsible for the development of the disease or death. The paper was aimed to review the risk factors associated with the progression and proliferation of Covid-19.*

Keywords: *Covid-19, Infections, Risk factors, Virus*

1. Introduction

The coronavirus disease 2019 (COVID-19) originated from Wuhan (Hubei state, China), carrying similar DNA structure to SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) has spread throughout the world and creating massive panic to the human life [1,2]. The disease has the worst feature to transmit from person to person [3], considering this feature and its lofty infection rate on January 30, 2020, the World Health Organization (WHO) declared COVID-19 as a global emergency. To date, it has infected more than 34 million people and over 1 million have died. As no proven treatment/medicine or vaccine is available to date [4] the harm of COVID-19 has already overtaken SARS and MARS [5].

Although the infection rate is very high, all the patients getting infected by this disease don't always die. The global recovery rate is about 75.2% and the death rate is about 2.96% until October 4, 2020. This information suggests that there may be some factors that influence the risk of death or critical medical states of the patients. That's why it is important to identify and estimate such risk factors to predict the severe complication of the patients for avoiding or to minimize the severity [6]. Patients with COVID-19 present primarily with various symptoms like fever, cough, dyspnea, myalgia, and fatigue [7,8]. Although most of the COVID-19 infected patients are thought to be recovered after few days, male patients, older patients (age greater than 60 years) and patients with various chronic diseases may have fatal outcomes [9]. Several factors are responsible for the severity and mortality of COVID-19 disease. From different studies, it had been found that patients with co-morbidities such as hypertension, diabetes mellitus, acute respiratory distress syndrome (ARDS), cardiovascular disease, cancer, COPD, asthma, renal disease, kidney disease, liver disease, hepatic disease, pneumonia, obesity, and also for the history of smoking were responsible for the development of the disease or death [10,11,12].

2. Global Distribution of Covid-19

According to World Health Organization Coronavirus (Covid-19) Dashboard updated 04th October, 2020, a total number of 34,804,348 cases of COVID-19 infection have been

confirmed worldwide, with a total of 1,030,738 deaths. In addition, over 216 countries and territories have reported at least a case of COVID-19 infection. The most countries with the highest burden of the infection include the United States of America (7,256,234), India (6,549,373), Brazil (4,880,523), Russia (1,215,001), Columbia (841,531) Peru (821,564) and South Africa (679,716) [13] All the continents of the world have reported at least a case. The Americas region has the highest number of reported cases while Western pacific region has the least number of COVID-19 infections. Table 1 below represents the regional number of confirmed COVID-19 cases as of 4th October, 2020.

Table1. *Number of confirmed COVID-19 and death cases as of 4th October, 2020 According to Region*

Region	Confirmed cases	Total death
Africa	1,198,550 (03%)	26,264 (03%)
Americas	16,990,036 (49%)	568,358 (55%)
Eastern Mediterranean	2,585,780 (07%)	63,156 (06%)
Europe	6,187,384 (18%)	240,148 (23%)
South-East Asia	7,335,273 (21%)	119,167 (12%)
Western Pacific	625,642 (02%)	13,632 (01%)
Others	741 (<01%)	13 (<01%)
Globally	**34,804,348**	**1,030,738 (100%)**

3. PATHOPHYSIOLOGY

COVID-19 can affect the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs) [14]. The lungs are the organs most affected by COVID-19 because the virus accesses host cells via the enzyme Angiotensin-converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells of the lungs [15]. The virus uses a special surface glycoprotein called a "spike" to connect to ACE2 and enter the host cell [16]. The density of ACE2 in each tissue correlates with the severity of the disease in that tissue and some have suggested decreasing ACE2 activity might be protective [17], though another view is that increasing ACE2 using angiotensin II receptor blocker medication could be protective [18]. As the alveolar disease progresses, respiratory failure might develop and death may follow [19]. SARS-CoV-2 may also cause respiratory failure through affecting the brain stem as other coronaviruses have been found to invade the Central Nervous System (CNS). While virus has been detected in cerebrospinal fluid of autopsies, the exact mechanism by which it invades the CNS remains unclear and may first involve invasion of peripheral nerves given the low levels of ACE2 in the brain [20]. The virus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium [21] as well as endothelial cells and enterocytes of the small intestine [10].

The virus can cause acute myocardial injury and chronic damage to the cardiovascular system [22]. An acute cardiac injury was found in 12% of infected people admitted to the hospital in Wuhan, China, and is more frequent in severe disease [23]. Rates of cardiovascular symptoms are high, owing to the systemic inflammatory response and immune system disorders during disease progression, but acute myocardial injuries may also be related to ACE2 receptors in the heart [22]. ACE2 receptors are highly expressed in the heart and are involved in heart function [22,24]. A high incidence of thrombosis and venous thremboembolism has been found in ICU patients with COVID-19 infections, and may be related to poor prognosis [25]. Blood vessel dysfunction and clot formation (as suggested by high D-dimer levels) are thought to play a significant role in mortality, incidences of clots leading to pulmonary embolisms and ischaemic events within the brain have been noted as complications leading to death in patients infected with SARS-CoV-2. Infection appears to set off a chain of vasoconstrictive response within the body, constriction of blood vessels within the pulmonary circulation has also been posited as a mechanism in which oxygenation decreases alongside the presentation of viral pneumonia [26]. Another common cause of death is complications related to the kidneys [26]. Early reports show that up to 30% of hospitalized patients both in China and in New York have experienced some injury to their kidneys, including some persons with no previous kidney problems [27]. Autopsies of people who died of COVID-19 have found diffuse alveolar damage (DAD), and lymphocyte-containing inflammatory infiltrates within the lung [28].

4. IMMUNOPATHOLOGY

Although SARS-CoV-2 has a tropism for ACE2-expressing epithelial cells of the respiratory tract, patients with severe COVID-19 have symptoms of systemic hyper inflammation. Clinical laboratory findings of elevated IL-2, IL-7, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon- γ inducible protein 10 (IP-10), monocyte chemo-attractant protein 1 (MCP-1), Macrophage inflammatory protein 1-α (MIP-1α) and tumor necrosis factor-α (TNF-α) indicative of cytokine release syndrome (CRS) suggest an underlying immunopathology (64). Additionally, people with COVID-19 and acute respiratory distress syndrome (ARDS) have classical serum biomarkers of CRS, including elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and ferritin [29]. Systemic inflammation results in vasodilation, allowing inflammatory lymphocytic and monocytic infiltration of the lung and the heart. In particular, pathogenic GM-CSF-secreting T-cells were shown to correlate with the recruitment of inflammatory IL-6-secreting monocytes and severe lung pathology in COVID-19 patients [30]. Lymphocytic infiltrates have also been reported at autopsy [28].

5. COVID-19 ASSOCIATED RISK

5.1. Age

Age and gender are well-established risk factors for severe COVID-19 outcomes: over 90% of the COVID-19-related deaths in the UK have been in people over 60, and 60% in men [31]. According to Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) mortality increases with age, with the highest mortality among people over 80 years of age. Recent studies also reported that elderly contacts were more likely to encounter COVID-19 infection [32,33]. According Nigeria Centre for Diseases Control, subjects within 31 – 40 years age category are more susceptible to contracting the disease in Nigeria which accounted for 24%. It however, said more death have been recorded among people of 60 years and above. Higher mortality among older people in Nigeria is due to co-morbidity from diseases such as diabetes, hypertension, asthma and cardiovascular diseases [34]. The immunity of the age may be weaker than younger adults, making them more susceptible to infection. Therefore, more efforts are needed to protect the elderly from the infection of COVID-19.

5.2. Co-Morbidities

Various pre-existing conditions have also been associated with increased risk. For example, the Chinese centre for disease control and prevention reported in a study of 44,672 individuals (1,023 deaths) that cardiovascular disease; hypertension, diabetes, respiratory disease and cancers were associated with an increased risk of death [35]. Most of those who die of COVID-19 have pre-existing (underlying) condition, including hypertension, diabetes mellitus, cancer, obesity, and cardiovascular disease [36]. According to March data from the United States, 89% of those hospitalized had preexisting conditions [37]. The Italian Istuto Superiore di Sanita reported that out of 8.8% of deaths where medical chart were available, 96.1% of people has at least one comorbidity with the average person having 3.4 diseases [38]. According to this report the most common comorbidities are hypertension (66% of deaths), type 2 diabetes (29.8% of deaths), ischemic heart disease (27.6% of deaths), atrial fibrillation (23.1% of deaths) and chronic renal failure (20.2% of deaths). Most critical respiratory comorbidities according to the CDC are: moderate or severe asthma pre-existing COPD, pulmonary fibrosis, cystic fibrosis [38]. A UK cross-sectional survey of 16,749 patients who were hospitalized with COVID-19 showed that the risk of death was higher for patients with cardiac, pulmonary and kidney disease, as well as cancer, dementia and obesity [39]. Obesity was associated with treatment escalation in a French intensive care cohort [40] (n = 124) and according to him, the odds of developing severe COVID-19 were seven times higher in patients with obesity.

A systematic review [41] indicated that people with diabetes were up to three times more likely to have severe symptoms or die from COVID-19, and the situation is likely to be worse for people with uncontrolled diabetes [42]. A meta-analysis showed that hypertension; cardiovascular and cerebrovascular disease increased the odds for severe COVID-19 by 2.3, 2.9 and 3.9 times, respectively [43]. Another meta-analysis indicated that hypertension increased the risk of mortality from COVID-19 by 3.5 times [29]. In a meta-analysis, patients with chronic obstructive pulmonary disease (COPD) were at increased risk of severe complications or death from COVID-19 [44].

A study in the United Kingdom suggested that the presence of respiratory disease, including

asthma, increased patients' risk of mortality from COVID-19 [45]. Cancer patients are more likely to experience severe COVID-19 [46]. A study in Wuhan, China, showed that the mortality rate from COVID-19 was significantly increased in patients with cancer and was particularly high among those with blood cancers [47].

5.3. Gender

Early reviews of epidemiologic data showed greater impact of the pandemic and a higher mortality rate in men in China and Italy [2,48]. The Chinese Center for Disease Control and Prevention reported the death rate was 2.8% for men and 1.7% for women [2]. Later reviews in June 2020 indicated that there is no significant difference in susceptibility or in CFR between genders [49,50]. One review acknowledges the different mortality rates in Chinese men, suggesting that it may be attributable to lifestyle choices such as smoking and drinking alcohol rather than genetic factors [51]. Sex-based immunological differences, lesser prevalence of smoking in women and men developing co-morbid conditions such as hypertension at a younger age than women could have contributed to the higher mortality in men [52]. In Europe, 57% of the infected people were men and 72% of those died with COVID-19 were men [53]. As of April 2020, the US government is not tracking sex-related data of COVID-19 infections [54]. Research has shown that viral illnesses like Ebola, HIV, influenza and SARS affect men and women differently [54].

According to Nigerian Centre for Disease Control (NCDC), as of 12th July 2020, out of 32,558 cases recorded, 21,385 (66%) are male while 11,173 (34%) are females. Similar study conducted by Frontier in Public Health Study in China showed that more men than women were susceptible to suffering severe Covid-19 complication. According to them, higher incidence in men for most of the diseases could correlate with general demographic fact of a shorter life expectancy in men when compared to women in China and world in general. A Professor of Molecular Microbiology and Immunology at John Hopskins Bloomberg School of Public Health (Sabra Klein) stated that there is greater immune response in female as compared to men and this greater immunity can be a blessing in many cases for women [55]. In addition to that; in Nigeria, higher incidence among men may be attributed to the high exposure of men as most of the women are house wives and always at home. Therefore, the women are less expose to the environment in Nigeria. According to medical experts, Covid-19 mainly affects the immune system, and there is ongoing research in Nigeria in understanding the cause of the increased rate of infections in Men.

5.4. Smoking and Alcohol

In a meta-analysis [44], smokers were 1.5 times more likely to have severe complications from COVID-19 and had a higher mortality rate. Evidence stemming from meta-analysis of several smaller research papers also suggests that smoking can be associated with worse patient outcomes [56]. When someone with existing respiratory problems is infected with COVID-19, they might be at greater risk for severe symptoms [38]. Alcohol impairs the body's ability to fight infections such as COVID-19 [57]. Even a single heavy drinking session can measurably reduce immune function. Intoxication can also interfere with taking precautions against infection.

5.5. Physical Inactivity

Physical activity provides multiple short- and long-term health benefits, including improving the immune system, stress and anxiety [58]. Physical activity is also associated with prevention of heart disease, hypertension, diabetes and overweight and obesity, which are risk factors for severe COVID-19 disease [59].

5.6. Pollution

A relation between exposure to air pollution and mortality from COVID-19 has been hypothesized [60]. Air pollution compromises lung function, which increases the risk for vulnerability to respiratory infection, including COVID-19.

6. Conclusion

The present review revealed that several factors are responsible for the severity and mortality of COVID-19 disease. It had been found that patients with comorbidities such as hypertension, diabetes mellitus, acute respiratory distress syndrome (ARDS), cardiovascular disease, cancer, hepatic disease, pneumonia, obesity, and also for the history of smoking and drinking alcohol were responsible for the development of the disease or death. Mortality rate among hospitalized COVID-19 patients was high in male gender and older aged patients.

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