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Risk Factor of COVID-19

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Abstract

Sever acute respiratory syndrome - corona virus-2 responsible for ongoing pandemic worldwide and significantly high number of morbidity and mortality still recorded, SARS COV-2 causes respiratory disease resulting from a life-threatening.

The aim of this study to investigate the correlation between risk factors which can increase the severity and incidence of COVID-19 through reviewing several studies.

This is a review study to assess risk factors of severity or death for covid-19 , Unstructured searches using the terms clinical findings," "clinical features," "clinical characteristic," "novel coronavirus," "covid-19," "SARS-Cov-2," "ABO" "comorbidity disease " , "Age", "Gender" were performed to identify articles written in English available on PubMed.

From this review we concluded that the infection rate in COVID-19 was noticed in old age group more than other age groups and it's often severing form. The most infection with COVID-19 was seen in male more than female. The Patients with COVID-19 infection who have underlying diseases (e.g. DM, Hypertension, cardiovascular and chronic lung disease) have a higher risk of developing the disease and they are more likely to die from the virus infection. The A blood group have a higher morbidity, mortality and hospitalization with COIVD-19 infection than non-A blood group.

1 Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious respiratory disease resulting from a life-threatening novel coronavirus, sever acute respiratory syndrome - corona virus-2 (SARS-CoV-2). As of February 20, 2021, there have been 110,743,440 confirmed cases and 2,452,437 deaths by the SARS-CoV-2 disease worldwide (CSSE, 2021).

The genome structure of CoVs is a non-segmented, positive-sense single-stranded RNA (+ssRNA). The genome size ranges from (27 to 32 kb) a cap structure at the 5′ end followed by a reader sequence of about 70 bases, several ORFs coding various proteins, and a non-translated region including a poly-A sequence at the 3′ end (Khailany *et al*., 2020).

Sever acute respiratory syndrome - corona virus-2 can be transmitted through respiratory droplets and direct contact, while the main transmission route of SARS-CoV-2 is aerosols, a recent experiment conducted with recovering patients found that SARS-CoV-2 can also exist in the patient's stool, suggesting that the fecal-oral route may be a route of transmission (Grayson *et al*., 2017).

The SARS-CoV-2 infection mainly presents flu-like symptoms such as cough, fever, fatigue and myalgia, patients may initially present with diarrhea and nausea a few days before developing a fever, which suggests that fever, is dominant but not the premier

symptom of infection. A small number of patients can have headache or hemoptysis (Wang *et al*., 2020). The clinical presentation of SARS-CoV-2 start within 14 days of exposure however; in most cases symptoms present after about 5 days and symptom onset is within 11.5 days in 97.5% of individuals (Lauer *et al*., 2020). Clinical data show that an increasing number of SARS-CoV-2 patients present circulatory symptoms (palpitations, chest tightness, short of breath) as the initial symptoms (Huang *et al*., 2020).

In, SARS-CoV-2 the inflammatory cytokine storm is closely related to the development and progression of acute respiratory distress syndrome (ARDS). The serum levels of cytokines are significantly increased in patients with ARDS, and the degree of increase is positively correlated with mortality rate (Parsons *et al*., 2005).

Several study show high level of pro-inflammatory cytokine in patient with SARS COV-2Patients infected with SARS-CoV-2 these include (IL-1, IL-2, IL-6, IL8, IL-17, G-CSF, GM-CSF) and chemokines (IP10 and MCP-1 in the sera during the disease, and may play a key role in the development of lung dysfunction by leading to the accumulation of immune cells within the lungs (Runfeng *et al*., 2020; Shi *et al*., 2020; Cao, 2020).

There is emerging evidence supporting the role of interleukin -17 (IL-17) in SARS-CoV-2 pathogenesis, including a report on the first

anatomopathologic lung analysis with a high number of T helper-17 lymphocytes in the alveolar space (Xu *et al*., 2020).

Sever acute respiratory syndrome-2 infection induces immunoglobulin (IgG) production against nucleocapsid (N) protein that can be detected by serum as early as day 4 after the onset of disease and with most patients seroconverting by day 14 (Hsueh, *et al* 2004; Liu, *et al* 2006).

There are around 162 vaccine candidates are currently in the preclinical evaluation, and 52 are in clinical development. These strategies include inhibition of S protein, proteases, mRNA, RNA-dependent-RNA-polymerase, whole virus vaccines, and antibody vaccines (Dutta, 2020). Currently, there is no available drug for SARS-CoV-2 , but many vaccines have been discovered; two of them are mRNA vaccine (moderna vaccine and Pfizer-bioNTech) (Wang *et al*., 2020), three of them are viral vector vaccine (Oxford-AstraZeneca and Gamaleya) (Folegatti *et al*., 2020) and finally inactivated vaccine (Sinopharm) (Xia *et al*., 2021).

the incidence and severity of COVID-19 correlate with risk factors and comorbidities, such as older age, cancer, obesity, cardiovascular diseases and diabetes linked to immune senescence, immunosuppression or immunopathology's (Wu et al.,2020; Mehta et al.,2020).

The clinical forms of COVID-19 are heterogeneous, according to the latest studies. At the time of admission, 20–51% of patients had at least one comorbidity, the most common of which were diabetes (10–20%), hypertension (10–15%), and other cardiovascular and cerebrovascular disorders (7–40%)(Kui et al., 2020).

The aim of this study to investigate the correlation between risk factors which can increase the severity and incidence of COVID-19 through reviewing several studies.

Methods

We conducted a review to assess studies looking for risk factors of severity or death for covid-19 , Unstructured searches using the terms clinical findings," "clinical features," "clinical characteristic," "novel coronavirus," "covid-19," "SARS-Cov-2," "ABO" "comorbidity disease " , "Age", "Gender" were performed to identify articles written in English available on PubMed.

Risk factor

1-Age

Advancing age is increasingly recognized as one of the strongest predictors for severe SARS-CoV-2 (Zhou *et al*., 2020). Older adults (aged above 60 years) are at increasing risk of contracting severe SARS-CoV-2 with higher complication and case fatality rates (Verity *et al*., 2020). Previously, older age has been reported as an important independent predictor of mortality in SARS and MERS (Hong *et al*., 2018).

Although age has emerged as the most important risk factor for adverse health outcomes related to the development of the cytokine storm and mortality, some younger individuals also fall gravely ill and develop similar cytokine storm pathology with COVID-19 (Qi *et al*., 2018).

Goldstein *et al*., (2021) report that younger adults, particularly those younger than 35 years are often have high incidence of SARS-CoV-2 infection in the community and the mortality rate in very elderly is significantly higher than elderly using serological test in United Kingdom Also study in china done by Liu *et al*, (2020) included 4880 confirmed cases SARS COV-2 infection by using real time PCR all patient were divided into six age group and the result was most infection within young age group as following : 482 (18-29) years ,

1097 (30–39) , 841 (40-49) years, 1011 (50–59) years, 886 (60–69) years, > 70 (563) years.

On other hand, Xu (2020) show that elderly people more susceptible to the more severe forms of the disease, Wu and McGoogan (2020) demonstrate that the case-fatality rate of patient within aged 70 to 79 years was 8.0% compared to patient within aged 80 years and older where it was 14.8%, Yang *et al*., 2020 reported that older patients (> 65 years) with comorbidities and ARDS are at increased risk of death.

Aging is associated with reduced in adaptive and innate immunity activity (Lutz and Quinn 2012, Golomb et al. 2015, Wong and Goldstein 2013).and with adverse age the body is fair to protect itself from viral and other infection (van , 2014). Replacement of skin cells and sweat production decreases with aging which is the first line of protection in our body immune system (Chilosi et al. 2014). DC which is way of liked between innate and adaptive immunity their function is decreased with advance age (Gupta, 2014).

The age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replication and more prolonged proinflammatory responses, potentially leading to poor outcome (Opal et al., 2005)

2-Gender

Accumulating data also show the existence of a gender-associated predisposition to SARS-CoV-2, with men being more prone to develop severe disease than women, studies in Saudi first one done by Alsofayan *et al.* (2020) found that among 1519 confirmed SARS COV-2 the rate of infection in male was 54.4% , the second report that 80% from confirmed cases were males (Al-Omari et al., 2020) and the third one also found 66% from infection with SARS-C0V-2 were males (Barry et al., 2020) . Also study in Iran done by Shahriarirad *et al*, (2020) found that 62.8% were male and significantly higher than female as their percentage was. 48.2% , study in Pakistani by Khan *et al*, (2020b) found that infection with SARS COV-2 male 71.12% significantly higher than female 28.88%. Also in china the male hah significantly high rate of infection than female (Liu et al., 2020). Chen et al., (2020), Huang et al., (2020) and Wang et al., (2020) in Wuhan China, Another study done by Guan et al., (2020) who revealed that males at risk of infection than females as their percentage 51.1% and female 49.9% in Wuhan-China,

possible explanations of male predominance among SARS-CoV-2 patients may be differences in exposure, smoking behavior, other lifestyle factors, differences in chromosomal ACE2 expression, ACE2 expression in testicular tissue, sex hormone-driven immune system regulation, or gender differences in renin-angiotensin aldosterone (RAAS) regulation (Cai, 2020). Other biological factors may influence the sex-bias observed in this study, expression of

angiotensin converting enzyme 2 receptors which facilitate SARS-CoV-2 viral entry and human to human transmission (Wan et al., 2020). Also, the different between the sexes, Oestradiol may influence ACE2 expression, and the gene for ACE2 is located in the X chromosome (Culebras and Hernández, 2020). Which may render it susceptible to escaping X-inactivation in women. The observation that women with COVID-19 show better outcomes compared to men and that post-menopausal women are those at higher risk of severe COVID-19 is consistent with the possibility that estrogens could protect females from severe COVID-19 (Stelzig et al., 2020). High testosterone levels could upregulate transmembrane serine protease 2 (TMPRSS2), facilitating the entry of severe acute respiratory syndrome coronavirus 2 into host cells via angiotensin-converting enzyme 2.

3- Comorbidity diseases

An outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world (Bogoch *et al*., 2020) .The initial symptoms of COVID-19 mainly include fever, cough, myalgia, fatigue, or dyspnea. In the later stages of the disease, dyspnea may occur and gradually develop into acute respiratory distress syndrome (ARDS) or multiple organ failure. (Huang et al., 2020). Patients with COVID-19 infection have shown that people with underlying diseases

not only have a higher risk of developing the disease but also are more likely to die from the virus infection (Verity *et al*., 2020).

High-risk patients requiring hospitalization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are those over 60 years old, males, obese, smokers, and those with common comorbidities including hypertension, cardiovascular disease, diabetes, and chronic lung disease Immunocompromised and cancer patients are also at greater risk. In one meta-analysis, the relative risk for experiencing severe versus nonsevere COVID-19 disease was 58%, 59%, and 71% higher in patients with hypertension, respiratory disease, and cardiovascular disease, respectively. .(Yang et al., 2020)

According to the latest studies. At the time of admission, 20–51% of patients had at least one comorbidity, the most common of which were diabetes (10–20%), hypertension (10–15%), and other cardiovascular and cerebrovascular disorders (7–40%). Liu *et al*., 2020; Chen *et al*., 2020)

The factors other than age may influence the course and outcome of the disease in these patients, two conditions appear to play a major role. The first is represented by the pre-existing health conditions or comorbidities. Patients with pre-existing pathological diseases and in particular those affected by multiple comorbidities die more frequently than those with no or few comorbidities. In other words, COVID-19, as other community-acquired pneumonias, acts as

terminal event that complicates long-term illnesses. This is in agreement with previous studies demonstrating that the presence of any comorbidity is associated with increased risk of poorer clinical outcomes. (Guan et al., 2020)

Diabetes Mellitus (DM) is one of the most prevalent chronic conditions with devastating multi-systemic complication and was estimated to have inflicted 463 million people in 2019 Saeedi *et al.*, 2019. It is not yet known whether people with DM are more susceptible to COVID-19, but several studies have reported the association between severe COVID-19 infection with DM Zhou *et al.*, 2020; Guo *et al.*, 2020). It was postulated that the angiotensin converting enzyme 2 (ACE2) may be the plausible explanation of this association (Ma and Holt, 2020)

It is not yet known whether people with DM are more susceptible to COVID-19, but several studies have reported a greater risk of severe COVID-19 in diabetic patients Zhou et al., 2020; Guo et al., 2020).Diabetic individuals have a greater risk of respiratory infections due to compromised immune system, especially the innate immunity (Pal and Bhansali, 2020) Even transient hyperglycaemia may temporarily affect innate immune responses to infection (Jafar *et al.*, 2016). It was hypothesized that ACE2 may be the key pathfinder of COVID-19 severity in diabetic individuals (Ma and Holt, 2020)

Dysfunctional pro-inflammatory cytokine responses in diabetic patients might also be the underlying cause of severe COVID-19 (Maddaloni and Buzzetti, 2020)

Diabetic patients have been shown to have an elevated pro-inflammatory cytokine level, in particular IL-1, IL-6 and tumor necrosis factor (TNF)-α ,Different markers, including C-reactive protein, fibrinogen and D-dimer were also found to be elevated in diabetic patients who contracted COVID-19, this condition may further exaggerate the cytokine storms in COVID-19 leading to a more severe disease (Mehta *et al*., 2020)

4-Blood group

The blood group system (ABO) includes mainly the A and B antigens as well as corresponding antibodies to them. On chromosome 9q34.1–34.2, the antigen-encoding gene is located. It consists of the alleles of A, B and O, There are 4 genetic phenotypes in total and (A, B, O, and AB blood types)(Vasan *et al*., 2016;).

Differences in antigen expression in the blood group can increase or decrease the sensitivity of the host to many infections.by acting as receptor or co-receptor for virus, parasite or other microorganism (Cooling, 2015).

Differences in blood group antigen expression can increase or decrease host susceptibility to many infections. Blood group antigens can play a direct role in infection by serving as receptors and/ or

coreceptors for microorganisms, parasites, and viruses. In addition, many blood group antigens facilitate intracellular uptake, signal transduction, or cell adhesion through the organization of membrane microdomains. Blood group antigens can modify the innate immune response to infection. Amundadottir *et al*., 2009

In one study included 187 patients with COVID-19 were The ABO blood group distribution was significantly related to dyspnea. Patients with type A, B, and O blood were less likely to presentwith dyspnea [patients with dyspnea had type A (42.03%), type B (15.87%), type O (31.71%), and type AB blood (50.00%), Wu et al., 2020

Another study also revealed that blood group A patients were at higher risk of hospitalization following SARS-CoV-2 infection, while blood group O patients had lower risk, which suggested that the ABO blood type could be used as a biomarker to predict the risk of SARS-CoV-2 infection Li *et al*., 2020

Another studies, in china by Zhao *et al*., 2020 found that SARS COV-2 patients who had blood type A increased risk of mortality than non A. Li *et al*., 2020 demonstrate that SARS COV-2 patients have type A at increased level of hospitalization followed infection. Zeng *et al*., 2020 in USA and Barnkob et al. 2020 in Denmark indicate that individuals with type A more susceptible to infection than other one else but not for hospitalization.

Conclusions

It could be recommended from the presented study that.

1. The infection rate in COVID-19 was noticed in old age group more than other age groups and it's often severing form.
2. The most infection with COVID-19 was seen in male more than female
3. The Patients with COVID-19 infection who have an underlying diseases (e.g DM , Hypertension , cardiovascular and chronic lung disease) have a higher risk of developing the disease and they are more likely to die from the virus infection.

The A blood group have a higher morbidity, mortality and hospitalization with COIVD-19 infection than non-A blood group.

Recommendations

1. Further designed studies with large-sample size are required to investigate the prevalence of SARS COV-2 co-infection with microorganisms.
2. Furthermore, the proportion mortality among patients infected with SARS-CoV-2 varied based on geographical location and ages.
3. Special attention should be addressed toward, asymptomatic carriers and workers in health care facilities as they play a key role in disease transmission.

4. Future study to assess the risk factor of mortality and hospitalization in SARS COV-2 infection in Iraq.

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