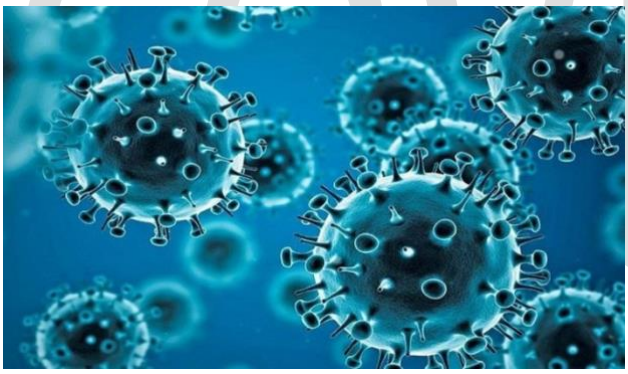
Republic of Iraq
Ministry of Higher Education
and Scientific Research
Diyala University
College of Medicine

Risk Factors of COVID-19



Presented by:
Zainab Ahmed Abass

Supervised by:
Dr. Hiba Hadi Rasheed

2022 A.D. **1443 A.H.**

بسم الله الرحمن الرحيم

((انزل الله عليك الكتاب والحكمة وعلمك ما لم تكن تعلم وكان فضل الله عليك عظيما))

صدق الله العلي العظيم

(سورة النساء الآية 113)

Acknowledgment

In the name of Allah, the most merciful, the most compassionate.

I would like to thank God for his mercy and grace, and i hope that God will accept this work with good acceptance

I would like to express our sincere gratitude, thanks and great appreciation for my supervisor Dr.Hiba Hadi, for her valuable and helpful advice and suggestions she provided and all her efforts made to complete this research.

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.

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.

Entry and life cycle of coronaviruses

One can think of viruses as molecular nanomachines that take over the host cell and force it to produce numerous copies of themselves. Even though, the replicative life cycle of viruses varies greatly depending on the species and the category of the virus. It consists of six basic stages, which are attachment, entry, un coating, replication, maturation and release (Harper, 2012).

The primary attachment of the virion to the host cell is beginning by interactions between the S protein and its receptor ACE2 which are found in various organs. such as lungs, kidneys, heart, and gastrointestinal tract. Thus assist viral entry into target cells. Following receptor binding, the virus must next get entry to the host cell cytosol, this is generally carried out by acid-dependent proteolytic cleavage of S protein by a cathepsin, Trans-membrane protease, serine2 (TMPRRS2) or another protease, after

that, fusion of the viral and cellular membranes, finally release of the viral genome into the cytoplasm (Walls *et al.*, 2020a).

In the following stage, direct translation of the positive-sense viral RNA genome leads to de novo synthesis of viral structural and NSPs. The NSPs, coded by the viral replicase gene, are responsible for the replication of the viral genome. This is followed by the "assembly" or “maturation” stage where newly synthesized viral structural proteins, viz. E, M and S are inserted into the endoplasmic reticulum-trans Golgi intermediate compartment (ERGIC). Viral genomes coated with the N protein then enter the ERGIC via budding to form mature virions (Khedkar and Patzak, 2020)

Mature virions then travel to the surface of the cell inside vesicles and exit the cells by exocytosis. A novel furin-like cleavage site has recently been discovered in SARS-CoV-2 spike protein. This cleavage site, which is absent in SARS-CoV, might be involved in viral egress and provide for the efficient spread of the virus in human population (Coutard *et al.*, 2020), Figure (2-2).

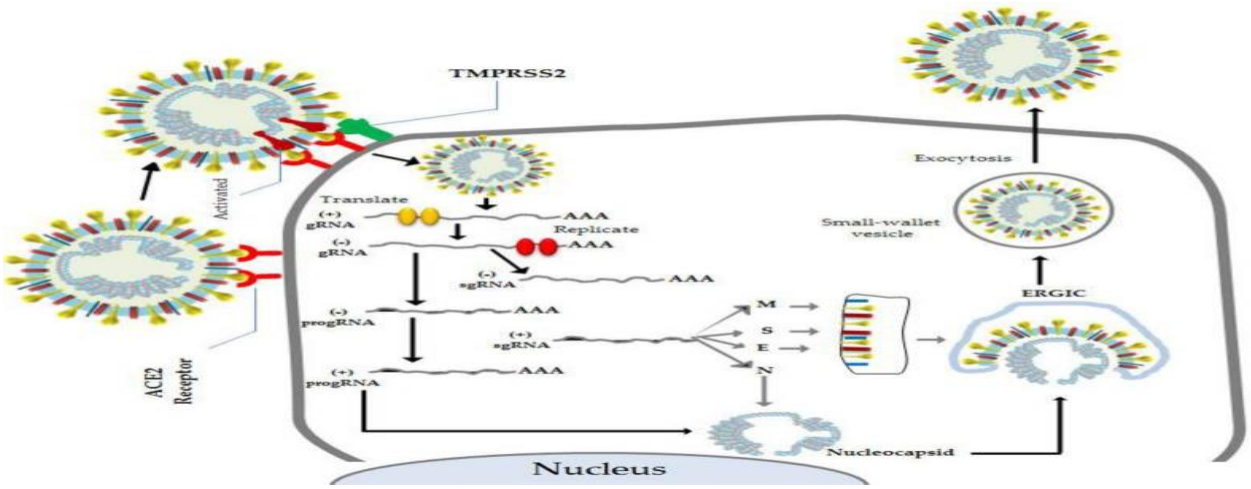


Figure (2-2): Replication of COV-2 in host cell (Astuti and Ysrafil, 2020).

Disease and symptoms

Since December 2019, an outbreak caused by a pathogen resulting in a respiratory disease occurred in Wuhan, China. The disease was termed coronavirus disease 2019 by the World Health Organization (WHO) and the causative agent was identified as severe acute respiratory syndrome coronavirus 2. The disease is now a global threat; and on 11 March 2020, WHO recognized the outbreak as a pandemic and SARS-CoV-2 has infected more than 372,757 and killed 16,231 people according to WHO (Organization, 2020).

Coronavirus is one of the major pathogens that primarily targets the human respiratory system. SARS-CoV-2 infection can be asymptomatic or be associated with the coronavirus disease 2019, which has a spectrum of respiratory clinical manifestations ranging from fever, dry cough, and dyspnea to pneumonia, pulmonary edema, acute respiratory distress syndrome, and multiple organ failures, requiring hospitalization in intensive care unit and leading to death in severe cases (Chen N., *et al.*, 2020).

Less common symptoms include headache, hemoptysis, nausea, vomiting, and diarrhea, although initially found in a small percentage of cases, an increasing number of patients present with diarrhea (Pan *et al.*, 2020).

The symptoms of COVID-19 may arise within 2 to 14 days after the infection, besides, in some cases, the diseases prevail after 27 days. However, Chinese researchers mentioned 5-2 days as an average incubation

period, which depends on the age, health and clinical conditions of the patients (Lauer *et al.*, 2020).

COVID-19, unlike other viruses, symptomatic infections are uncommon in children and, although not resistant, children are at low risk of severe disease. Based on current data, the mean case fatality rate for adults aged under 60 is estimated to be less than 0.2%, compared with 9.3% in those aged over 80. Even if comorbidities increased mortality risk by five times, risk would remain lower for younger people than for most older adults (Jordan, Adab and Cheng, 2020).

Older age, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were all associated with an increased risk of death.(Wu and McGoogan, 2020)

Transmission

COVID-19 is transmitted first, from person to person (direct contact) through respiratory droplets, these droplets can travel for distances 6 feet or less in air. Second, SARS-CoV-2 is likely transmitted through fomites (indirect contact) for the duration it is viable on environmental surfaces (Galbadage, Peterson and Gunasekera, 2020). Third, it is also likely transmitted through aerosols (indirect contact) for distances longer than 6 feet in the air.

To establish an infection, SARS-CoV-2 needs to first reach an entry point eyes (Lu, Liu and Jia, 2020), nose, or mouth on a susceptible host (Zhang H., *et al.*, 2020).

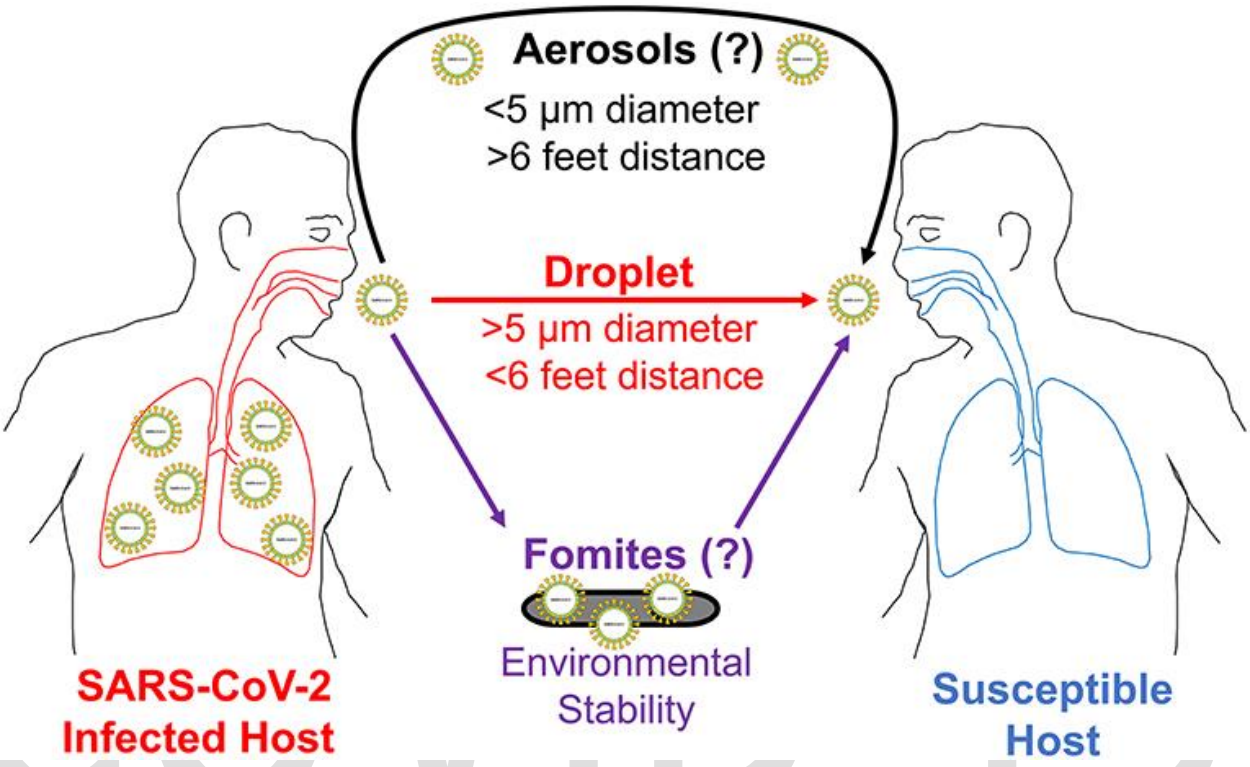


Figure (2-3): COV-2 modes of transmission (Galbadage, Peterson and Gunasekera, 2020)

Clinical features

COVID-19 (62%; diagnosis based on positive viral nucleic acid test result on throat swab samples), (22%; diagnosis based on symptoms and exposures only, no test was performed because testing capacity is insufficient to meet current needs). In these cases, no test was performed but diagnosis was made based on symptoms, exposures, and presence of lung imaging features consistent with coronavirus pneumonia, asymptomatic cases (1% diagnosis by positive viral nucleic acid test result

but lacking typical symptoms including fever, dry cough, and fatigue) (Wu and McGoogan, 2020).

Not everybody who is subjected to SARS-CoV-2 are infected and not every infected person gets severe respiratory illness. As a result, SARSCoV-2 infection can be roughly divided into three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load (Guan W., *et al.*, 2020).

Classification of COVID-19 patients

The severity of COVID-19 was defined based on the clinical features, laboratory testing and chest X-ray imaging, including asymptomatic infection, mild, moderate, severe and critical cases (Yuki, Fujiogi and Koutsogiannaki, 2020), which summarized in Table (2-2).

Table (2-2): Classification of COVID-19 patients (Gülsen, 2019)

Asymptomatic	COVID nucleic acid test positive. Without any clinical symptoms and signs and the chest imaging is normal.
Mild	outpatients and patients with mild clinical symptoms or lower or upper respiratory tract infections.
Moderate	patients requiring hospitalization, with lobar or

	multilobar pneumonia with/without the need for supplemental oxygen, or refractory to initial treatment.
Severe	patients who need ICU treatment, noninvasive or invasive mechanical ventilatory support, or with acute respiratory distress syndrome and/or non-pulmonary involvement.
Critical	patients who need immune-modulatory therapy or with multi-organ failure and/or cytokine storm.

Diagnosis of COVID-19

Clinical diagnosis of COVID-19 is mainly based on epidemiological history, clinical manifestations and some auxiliary examinations, such as nucleic acid detection, CT scan, immune identification technology (Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA)) and blood culture. However, the clinical symptoms and signs of patients infected with SARS-CoV-2 are highly atypical, including respiratory symptoms, cough, fever, dyspnea, and viral pneumonia. Therefore, auxiliary examinations are necessary for the diagnosis of COVID-19, just as the epidemiological history (Li X., *et al.*, 2020).

Current treatment strategies for COVID-19

There is currently no clinically proven specific antiviral agent available for SARS-CoV-2 infection (Huang, *et al.*, 2020). Just like SARS-CoV and MERS-CoV (De Wit *et al.*, 2016), the supportive treatment, including oxygen therapy,

conservation fluid management, and the use of broad-spectrum antibiotics to cover secondary bacterial infection, remains to be the most important management strategy (Huang, *et al.*, 2020).

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.

Discussion

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.

Conclusion and Recommendations

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 SA RS COV-2 infection in Iraq.

Reference

 Shahriarirad, R., Khodamoradi, Z., Erfani, A., Hosseinpour, H., Ranjbar, K., Emami, Y., Mirahmadizadeh, A., Lotfi, M., Yeganeh, B.S., Nejad, A.D. and Hemmati, A. (2020). Epidemiological and clinical features of 2019 novel coronavirus diseases (COVID-19) in the South of Iran. BMC infectious diseases, 20(1): 1-12.

 Al-Omari, A., Alhuqbani, W.N., Zaidi, A.R.Z., Al-Subaie, M.F., AlHindi, A.M., Abogosh, A.K., Alrasheed, A.K., Alsharafi, A.A., Alhuqbani, M.N., Salih, S. and Alhedaithy, M.A. (2020). Clinical characteristics of non-intensive care unit COVID-19 patients in Saudi Arabia: a descriptive cross-sectional study, J. Infect., 13(11): 1639-1644.

 Alsofayan, Y.M., Althunayyan, S.M., Khan, A.A., Hakawi, A.M. and Assiri, A.M.(2020). Clinical characteristics of COVID-19 in Saudi Arabia: A national retrospective study, Journal of Infection and Public Health, 13(7): 920-925.

 Amundadottir, L., Kraft, P., Stolzenberg-Solomon, R.Z., Fuchs, C.S., Petersen, G.M., Arslan, A.A., Bueno-de-Mesquita, H.B., Gross, M., Helzlsouer, K., Jacobs, E.J. and LaCroix, A. (2009). genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer, Nat. Genet., 41(9):986-990.

 Barnkob, M.B., Pottegård, A., Støvring, H., Haunstrup, T.M., Homburg, K., Larsen, R., Hansen, M.B., Titlestad, K., Aagaard, B., Møller, B.K. and Barington, T. (2020). reduced prevalence of SARS-CoV-2 infection in ABO blood group O, Blood Adv., 4(20):4990-4993.

 Barry, M., AlMohaya, A., AlHijji, A., Akkielah, L., AlRajhi, A., Almajid, F., Alsharidi, A., Al-Shahrani, F.S., Alotaibi, N.H., Alanazi, A. and Ghonem, L. (2020). Clinical characteristics and outcome of hospitalized COVID-19 patients in a MERS-CoV endemic area, Journal of epidemiology and global health, 10(3): 214

 Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Potential for global spread of a novel coronavirus from China. J Travel Med. 2020;27(2):taaa011.

 Cai, H., (2020). Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med, 8: e20

 Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., and Yu, T. (2020). epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan-China: a descriptive study, Lancet, 395(10223):507-513.

 Chilosi, M., Facchetti, F., Caliò, A., Zamò, A., Brunelli, M., Martignoni, G., Rossi, A., Montagna, L., Piccoli, P., Dubini, A. and Tironi, A. (2014). Oncogene-induced senescence

distinguishes indolent from aggressive forms of pulmonary and non-pulmonary Langerhans cell histiocytosis, Leuk Lymphoma, 55(11): 2620-2626.

 Cooling, L. (2015). Blood groups in infection and host susceptibility. Clinical microbiology reviews, Clin. Microbiol. Rev., 28 (3): 801–870.

 Culebras, E. and Hernández, F. (2020). ACE2 is on the X chromosome: could this explain COVID-19 gender differences, Eur. Heart J., 41(32): 3095-3095.

 Goldstein, E., Lipsitch, M., and Cevik, M. (2021). On the Effect of Age on the Transmission of SARS-CoV-2 in Households-Schools, and the Community, J. Infect. Dis., 223(3):362-369.

 Golomb, L., Sagiv, A., Pateras, I.S., Maly, A., Krizhanovsky, V., Gorgoulis, V.G., Oren, M. and Ben-Yehuda, A.(2015). Age-associated inflammation connects RAS-induced senescence to stem cell dysfunction and epidermal malignancy, Cell Death Differ., 22(11): 1764-1774.

 Guan, W.J., Liang, W.H., Zhao, Y., Liang, H.R., Chen, Z.S., Li, Y.M., Liu, X.Q., Chen, R.C., Tang, C.L., Wang, T. and Ou, C.Q., 2020. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Res J , 55(5).

 Guan, W.J., Liang, W.H., Zhao, Y., Liang, H.R., Chen, Z.S., Li, Y.M., Liu, X.Q., Chen, R.C., Tang, C.L., Wang, T. and Ou, C.Q., (2020). Comorbidity and its impact on 1590 patients with
COVID-19 in China: a nationwide analysis, Eur. Respir. J., 55; (5)

 Guo, W., Li, M., Dong, Y., Zhou, H., Zhang, Z., Tian, C., Qin, R., Wang, H., Shen, Y., Du, K. and Zhao, L., (2020). Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes/metabolism research and reviews, 36(7), p.e3319.

 Gupta, S. (2014). Role of dendritic cells in innate and adaptive immune response in human aging. Exp Gerontol 54(1): 47-52.

 Hong, K.H., Choi, J.P., Hong, S.H., Lee, J., Kwon, J.S., Kim, S.M., Park, S.Y., Rhee, J.Y., Kim, B.N., Choi, H.J. and Shin, E.C., (2018). Predictors of mortality in Middle East respiratory syndrome (MERS), *Thorax*, *73*(3): 286-289.

 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223): 497-506

 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan-China, Lancet, 395: 497-506.

 Jafar, N., Edriss, H. and Nugent, K., (2016). The effect of short-term hyperglycemia on the innate immune system. The American journal of the medical sciences, 351(2), 201-211.

 Khan, M., Khan, H., Khan, S. and Nawaz, M., 2020b. Epidemiological and clinical characteristics of coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study. Journal of medical microbiology, 69(8): 1114.

 Li, J., Wang, X., Chen, J., Cai, Y., Deng, A. and Yang, M.(2020). association between ABO blood groups and risk of SARS-CoV-2 pneumonia, Br. J. Haematol., 190(1):24-27.

 Li, J., Wang, X., Chen, J., Cai, Y., Deng, A. and Yang, M., 2020. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. British journal of haematology, 190(1), pp.24-27.

 Li. T, Wei, C., Li,W., Hongwei, F. and Shi, J. (2020b) Beijing Union Medical College Hospital on "pneumonia of novel coronavirus infection" diagnosis and treatment proposal (V2.0), Med. J. Peking Union Med. Coll. Hosp.,16(28):22.

 Liu, R., Han, H., Liu, F., Lv, Z., Wu, K., Liu, Y., Feng, Y. and Zhu, C., (2020). Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clinica. Chimica. Acta., 505:172-175.

 Lutz and Quinn. (2012) . Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. Aging-US., 4(8): 535-546.

 Ma, R.C.W. and Holt, R.I.G., (2020). COVID-19 and diabetes. Diabetic Medicine.

 Maddaloni, E. and Buzzetti, R., (2020). Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes/metabolism research and reviews, 36(7): e33213321.

 Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S. and Manson, J.J., 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet, 395(10229), pp.1033-1034.

 Opal, S.M., Girard, T.D. and Ely, E.W., 2005. The immunopathogenesis of sepsis in elderly patients. Clinical infectious diseases, 41(Supplement_7), pp.S504-S512. Gupta, S. (2014). Role of dendritic cells in innate and adaptive immune response in human aging. Exp Gerontol 54(1): 47-52.

 Pal, R. and Bhansali, A., 2020. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes research and clinical practice, 162.

 Qi, Y., Chen, X., Wu, N., Ma, C., Cui, X., and Liu, Z. (2018). identification of risk factors for sepsis-associated mortality by gene expression profiling analysis, Mol. Med. Rep., 17(4): 5350-5355.

 Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A.A., Ogurtsova, K. and Shaw, J.E., (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice, 157, 107843.

 Stelzig, K.E., Canepa-Escaro, F., Schiliro, M., Berdnikovs, S., Prakash, Y.S., and Chiarella, S.E. (2020). estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells, Am. J. Physiol. Lung Cell Mol., 318(6): L1280-L1281.

 Van Deursen, J.M. (2014). The role of senescent cells in ageing,Nature 509(7501): 439-446.

 Vasan, S.K., Rostgaard, K., Majeed, A., Ullum, H., Titlestad, K.E., Pedersen, O.B., Erikstrup, C., Nielsen, K.R., Melbye, M., Nyrén, O. and Hjalgrim, H., 2016. ABO blood group and risk of thromboembolic and arterial disease: a study of 1.5 million blood donors, Circulation, 133(15):1449-1457.

 Verity, R., Okell, L.C., Dorigatti, I., Winskill, P., Whittaker, C., Imai, N., Cuomo-Dannenburg, G., Thompson, H., Walker, P.G., Fu, H., and Dighe, A. (2020). estimates of the severity of coronavirus disease 2019: a model-based analysis, Lancet Infect. Dis., 20(6):669-677

 Wan, Y., Shang, J., Graham, R., Baric, R.S. and Li, F. (2020). Receptor recognition by the novel coronavirus from Wuhan-China: An Analysis Based on decade-long structural studies of SARS Coronavirus, J. Virol., 94, e00127-20.

 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, and Zhao Y. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan-China, JAMA, 323(11):1061-9.

 Wu, Y., Feng, Z., Li, P. and Yu, Q., 2020. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clinica Chimica Acta, 509, pp.220-223.

 Wu, Z., and McGoogan, J.M. (2020). characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China -summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, JAMA, 323(13):1239-42.

 Xu , Q.L. (2020). Frailty as an integrative marker of physiological vulnerability in the era of COVID-19, BMC Med., 18(1):333.

 Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q . (2020). Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis;94:91-5.

 Yang, J., Zheng, Y.A., Gou, X., Pu, K., Chen, Z., Guo, Q., Ji, R., Wang, H., Wang, Y., and Zhou, Y. (2020). Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis, Int. J. Infect. Dis., 94: 91-95.

 Yang, X., Yu, Y., Xu, J., Shu, H., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., and Wang, Y. (2020). clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respir Med., 8(5):475-81.

 Zeng, X., Fan, H., Lu, D., Huang, F., Meng, X., Li, Z., Tang, M., Zhang, J., Liu, N., Liu, Z. and Zhao, J. (2020). Association between ABO blood groups and clinical outcome of coronavirus disease 2019: Evidence from two cohorts. Infect. Genet. Evol., 84(1567-1348):104485

 Zhao, J., Yang, Y., Huang, H., Li, D., Gu, D., Lu, X., Zhang, Z., Liu, L., Liu, T., Liu, Y. and He, Y.(2020). relationship between the ABO Blood Group and the COVID-19 Susceptibility. Clin. Infect. Dis., ciaa1150.

 Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X. and Guan, L., (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet, 395(10229), 1054-1062.
 Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., and Guan, L., (2020). clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan-China: a retrospective cohort study, The lancet, 395(10229): 1054-1062.

 Grayson, S.A., Griffiths, P.S., Perez, M.K., and Piedimonte, G. (2017). detection of airborne respiratory syncytial virus in a pediatric acute care clinic, Pediatr. Pulmonol., 52(5): 684-688.

 Hsueh, P.R., Huang, L.M., Chen, P.J., Kao, C.L., and Yang, P.C. (2004). Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus, Clin. Microbiol. Infect., 10(12): 1062-1066.

 Lauer, S.A., Kyra, H.G., Qifang, B., Forrest, K.J., Qulu, Z., Hannah, R.M., Andrew, S.A., Nicholas, G.R., and Justin, L. (2020). The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application, Ann. Intern. Med., 172(9): 577-582.

 Liu, J., Zheng, X., Tong, Q., Li, W., Wang, B., Sutter, K., Trilling, M., Lu, M., Dittmer, U., and Yang, D. (2020). Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-CoV, J. Med. Virol., 92(5): 491-494.

 Liu, W., Fontanet, A., Zhang, P.H., Zhan, L., Xin, Z.T., Baril, L., Tang, F., Lv, H., and Cao, W.C. (2006). Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome, J. Infect. Di., 193(6): 792-795.
 Parsons, P.E., Eisner, M.D., Thompson, B.T., Matthay, M.A., Ancukiewicz, M., Bernard, G.R., and Wheeler, A.P. (2005). lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury, C**rit. Care. M**ed., 33(1): 1-6.

 Prompetchara, E., Chutitorn, K., and Tanapat, P. (2020) immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic, Asian Pac. J. Allergy Immunol., 38(1):1-9.

 Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., and Zhao, Y., 2020. Clinical characteristics of 138 hospitalized patients

with 2019 novel coronavirus–infected pneumonia in Wuhan- China, Jama., 323(11): 1061-1069.

 Xu, Z., Lei, S., Yijin, W., Jiyuan, Z., Lei, H., Chao,Z., Shuhong,L.,Peng, Z., Hongxia, L., Li, Z., Yanhong, T., Changqing, B., Tingting, Gao., Jinwen, Song., Peng, Xia., Jinghui, D., Jingmin, Z., and Fu-Sheng, W., (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet, 8(4):420-422.

 Prompetchara, E., Ketloy, C., and Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS-1 and MERS epidemic, Asian Pac. J. Allergy. Immunol., 38(1):1-9.

 Wang, F., Kream, R.M., and Stefano, G.B. (2020). An evidence-based perspective on mRNA-SARS-CoV-2 vaccine development, Med. Sci. Monit., 26: e924700.

 Folegatti, P.M., Ewer, K.J., Aley, P.K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E.A., and Dold, C. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial, Lancet, 396: 467-478.

 Dutta, A.K. (2020). Vaccine against covid-19 disease - Present status of development, Indian J. Pediatr., 87: 810-816.

 Xia, S., Zhang, Y., Wang, Y., Wang, H., Yang, Y., Gao, G.F., Tan, W., Wu, G., Xu, M., Lou, Z., and Huang, W., (2021). Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial, Lancet Infect. Dis, 21(1): 39-51.

 COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)". ArcGIS. Johns Hopkins University (2021).

 Khailany, R.A., Safdar, M. and Ozaslan, M. (2020) genomic characterization of a novel SARS-CoV-2. Gene reports, 19 :100682.

 Runfeng, L., Yunlong, H., Jicheng, H., Weiqi, P., Qinhai, M., Yongxia, S., Chufang, L., Jin, Z., Zhenhua, J., Haiming, J. and Kui, Z. (2020). lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2), *Pharmacological research*, 156: 104761.

 Shi, Y., Wang, Y., Shao, C., Huang, J., Gan, J., Huang, X., Bucci, E., Piacentini, M., Ippolito, G. and Melino, G. (2020). COVID-19 infection: the perspectives on immune responses, *Nature*, 27; 1451–1454

 Cao, X. (2020). COVID-19: immunopathology and its implications for therapy, *Nat. Rev. Immunol*., 20(5):269-270.

 Wu, C., Chen, X., Cai, Y., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y. and Song, J., (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine.;180(7):934–943

 Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., Manson, J.J. and HLH Across Speciality Collaboration, (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England), 395(10229), p.1033.

 Kui L, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J 2020; in press [https://doi.org/10.1097/CM9.0000000000000744].

 Vasan, S.K., K. Rostgaard, A. Majeed, H. Ullum, K.E. Titlestad, O.B. Pedersen, C. Erikstrup, K.R. Nielsen, M. Melbye, O. Nyren, et al., ABO blood group and risk of thromboembolic and arterial disease: a study of 1.5 million blood donors, Circulation 133 (15) (2016) 1449–1457 discussion 1457.

 Cooling, L., Blood Groups in Infection and Host Susceptibility, Clin. Microbiol. Rev. 28 (3) (2015) 801–870.