

Risk factors contributing in increased susceptibility and severity of COVID 19 infection during pregnancy.

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Abstract

Background: The corona virus disease 2019 (COVID-19) pandemic has spread globally and pregnant women are considerably prone to COVID 19 infection with increased maternal and perinatal complications.

Objective: This study aims to explore the risk factors that contribute in susceptibility and severity of COVID 19 infection among pregnant women.

Methods: A systematic search of articles relating to COVID 19 infection during pregnancy, was conducted, using PubMed, Scopus and Google scholar engine.

Results: A total of 168 articles were initially identified. Seventy-seven papers were excluded for failing to address the aim of the study. After screening titles and abstracts, ninety-one full-text articles were retrieved for eligibility analysis. Seventeen studies addressed the susceptibility related to pregnancy, twenty-two studies evaluated the associated comorbidities, nineteen focused on immune system, thirty-five articles concentrated on the risk of coagulopathy and eleven addressed more than one risk factor.

Conclusions: Pregnancy, associated comorbidities, modulated immune response during pregnancy and risk of coagulopathy are considerable risk factors contributing in COVID 19 pathogenesis among pregnant women and may predict the outcome.

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Original Manuscript

Risk factors contributing in increased susceptibility and severity of COVID 19 infection during pregnancy.

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Abstract: The corona virus disease 2019 (COVID-19) pandemic has spread globally and pregnant women are considerably prone to COVID 19 infection with increased maternal and perinatal complications.

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Conclusion: Pregnancy, associated comorbidities, modulated immune response during pregnancy and risk of coagulopathy are considerable risk factors contributing in COVID 19 pathogenesis among pregnant women and may predict the outcome.

Key words; “pregnancy” “corona virus” “COVID-19”, and “SARS-CoV-2”.

Introduction

COVID 19 or novel coronavirus (2019-nCoV) infection was declared as pandemic by the World

Health Organization on March 11, 2020 and resulted in marked increase in morbidity and fatality globally. Recent data released on 2nd of May 2020, has shown 3,402,160 of confirmed cases worldwide, deaths 239,623 individuals, recovered 1,083,943 subjects, mild cases 2,027,228 (98%) and 51,366 (2%) patients were seriously or Critically ill.(1) Likewise, in a weekly report of morbidity and mortality from United States of America, on March 28, 2020, confirmed a total of 122,653 of cases with COVID-19 infection, 2% these cases were found to be pregnant and about 3.8% were smokers. Approximately one third of these patients (smoking and pregnancy) (2,692, 37.6%), had at least one underlying chronic medical condition or risk factor: Diabetes mellitus (DM) (10.9%), chronic lung disease (9.2%), and cardiovascular disease (9.0%).(2) The most common symptoms at presentation were fever (75%) and cough (73%).(3) Higher percentage of DM and hypertension may be linked to the global increase in the prevalence, including some of developing countries.(4–7) Furthermore, the presence of one or more of comorbidities, would be reflected in severity of the disease and a higher percentage of hospital admission: in intensive care unit (ICU) (78%) and non-ICU hospitalizations (71%).(2) On the other hand, only (27%) COVID-19 patients who did not require hospitalization, were found to have at least one underlying medical condition.(2) Some clinical data, showed most cases presented in the 3rd trimester that hires potential risk for complications compared to few numbers of cases who presented in earlier gestational age with favorable outcome.(3,8) The rate of Cesarean section was considerable very high in this group of patients (92% -93%) compared to recorded successful vaginal delivery.(3,8) The case fatality rate has been estimated at around 3% for the novel coronavirus and it was too early to be able to put a percentage on the mortality rate because fatality rate can change as a virus can mutate.(9,10) A recent published study that recruiting 118 pregnant women with confirmed COVID 19 infection, found (92%) had mild disease, (8%) had severe disease (hypoxemia), and only one case required noninvasive mechanical ventilation. Interestingly, (94%) of them had been discharged, including all women with severe or critical disease without reported fatality.(8) Moreover, they reported only 3%

of pregnant women with confirmed SARS-CoV-2 infection who required maternal intensive care admission and successfully recovered with no confirmed fatalities.(8) Similarly, a study from China, reported a favorable risk of severe COVID 19 disease in (8%) of pregnant women compared with the risk in the general population (15.7%).(11) In one study that showed mild presentation of the disease in 368 (95.6%) of pregnant women, severe course in (3.6%) and critical in (0.8%). Interestingly, only one patient died from seventeen (4.4%) women who required management in an intensive care unit (ICU).(12) In contrast, the case fatality rate for SARS and MERS were 10% and 37% respectively. (13) Despite comparatively lower rate of fatality in SARS-CoV infection (10%), a relatively higher rate was registered among pregnant women (25%.(1,14) In a systematic review evaluating 385 pregnant women with COVID-19 infection, the perinatal complications were obtained, including preterm birth (15.2%) newborns, Low birth weight (7.8%) newborns, intrauterine fetal distress (7.8%) newborns and confirmed vertical transmission in (1.2%) of newborns.(12) In case series study, assessing nine pregnant women with severe COVID-19 disease, a considerable higher death rate was reported in seven cases.(15) For potential increase in the vulnerability of pregnant women and few papers addressing this issue during the current pandemic, I conducted this study to evaluate the possible risk factors that prone pregnant women to COVID 19 infection.

Method

A systematic search of studies focusing COVID 19 infection during pregnancy, was conducted without frame time limit, using PubMed, Scopus and Google scholar, with the key the words; “pregnancy” “corona virus” “COVID-19”, and “SARS-CoV-2”. The electronic database search generated 168 studies. Seventy-seven studies were excluded for not fulfilling the aim of the study, duplication, lacking proper citation, and language issue. Titles and abstracts were evaluated to identify eligibility for full screening. Studies that employed acceptable quantitative and/or qualitative methods, including randomized controlled trials, observational studies (such as cross-sectional, experimental, and interventional studies), review articles, editorials, reports, ideas, letters to the

editor and opinions were included. All studies focusing on the pathogenesis of COVID 19 among pregnant women, risk factors related pregnancy, effects of associated comorbidities, immune response, medications influence and risk of coagulopathy associated with COVID 19 were eligible for inclusion. Once all relevant articles had been determined, full-text manuscripts were retrieved for assessment. Then the studies were grouped according to the primary aims, risk related to pregnancy, associated comorbidities, immune response and risk of coagulopathy. This facilitated identification of proper articles that concentrated on specific topics and issues relevant to my objectives and enabled the retrieval of information.

Result

A total of 168 articles were initially identified. Seventy-seven studies were removed for not addressing the target of the study, duplication, lacking proper citations and language issue. After screening titles and abstracts, ninety-one full-text articles were retrieved for eligibility analysis. Seventeen studies addressed the susceptibility related to pregnancy, (8,9,12,14,16-28) twenty two studies evaluated the associated comorbidities, (11,28-48) nineteen focused on immune system, (8,20-22,49-63) thirty five article concentrated on the risk of coagulopathy (8,16,55,64-95) and eleven addressed more than one risk factor(8,9,11,12,14,16,20-22,28,55). The risk factors appear to have a predictor value for increasing susceptibility to COVID 19 infection and worsening the outcome among pregnant women.

Discussion

Pregnancy has some factors that may potentiate the vulnerability to COVID 19 infection and severity of presentation. From anatomical aspect, the size of the chest cavity is markedly, affected by the growing womb during pregnancy, leaving less space for the lungs to expand, especially in the last trimester. This explains why pregnant women often experience difficulty in breathing during mild episodes of chest infection and worsens if they had COVID-19 infection. (8,16,17) Similarly,

pregnant women are prone to respiratory pathogens and at risk of pneumonia compared with nonpregnant women due to physiological adaptations in pregnancy: airway edema, diaphragmatic elevation, increased oxygen consumption, and pregnancy-related immune-alterations.(18) Thus their tolerance to hypoxia is significantly impaired.(18) Furthermore, gestational rhinitis that affects one-fifth of healthy women in late pregnancy, is estrogen mediated hyperemia of the nasopharynx, leading to marked nasal congestion and rhinorrhea that may mask the coryzal symptoms of COVID-19 infection. This may lead to active viral shedding and increase risk of community transmission in low suspicious judgement for COVID 19 infection, besides resulting in late presentation of the disease. (17,19) Additionally, they are exposed to higher risk of other respiratory pathogens. (17) Given that, circulating higher levels of maternal estrogens and progesterone through most of gestation age, exert immunomodulatory effects that promote safety of pregnancy.(20,21) Progesterone's immune-adaptive response is characterized by promoting Th 2-type responses, increase expression of leukemia inhibitory factor, reducing levels of cytokines (IFN- γ , TNF- α , IL-5, and IL-10) and increasing levels of IL-4 production by CD8⁺ T cells.(20,21) Likewise, higher levels of prolactin, have stimulatory effects on cell-mediated, humoral immune responsiveness and may extend to include the innate immune effector cells.(22) Physiological and mechanical changes in pregnancy increase susceptibility to infections in general, particularly when the cardiorespiratory system is affected, will precipitate rapid progression to respiratory failure in pregnancy.(23) Previous report demonstrated 27% fatality among 1350 pregnant women who got the disease during the 1918 influenza pandemic.(16) Similarly, the SARS virus, had general case fatality of 25% among pregnant women and increased to 50% of those who required ICU admission.(14) In the 2009 H1N1 influenza virus outbreak, pregnant women had four times chance to be admitted with increased risk of complications compared with the general population.(24) Similar outcome may be extrapolated for COVID 19 infection among pregnant women in the light of earlier pandemic stage of COVID 19 and being related to corona virus family. Recently published clinal data linked pregnancy to increased

susceptibility to COVID 19 and hired potential risk for severe presentation.(19,25,26) The 3rd trimester appears to bring in a higher potential risk to contract the disease (64% -80%) compared to presentation in earlier gestational age which may favor better prognosis and outcome(8,9) Furthermore, the rate of documented cesarean section was very high (92%) compared to successful normal vaginal delivery (8%).(8) Another study documented almost similarly higher rate of cesarean sections (93%), (61%) the procedure was indicated of concern about the effects of Covid-19 on the pregnancy and (21%) were delivered premature.(9) In addition to clear documented perinatal complications related to COVID 19 disease.(12) In contrast, a systematic review reported only 3% of pregnant women with confirmed SARS-CoV-2 infection required intensive care management and no confirmed fatalities were reported.(8) Recently, the outcome of some studies lacked the clear evidence to consider pregnancy as a risk factor for more severe disease in women with COVID-19 (17,27,28) In the presence of many supporting evidences that documented increased susceptibility to COVID 19 infection, severe presentation, maternal and fetal complications, encourage us to consider pregnancy as potential risk that deserve vigilant and proper earlier management to improve the outcome.

Indeed, comorbidities such as diabetes, cardiac failure, or hypertension, have been identified as risk factors for severe COVID-19 infections in nonpregnant adults and also are considered additional risk factors for pregnant women to hire worse prognosis.(28) Among different comorbidities registered, hypertension (3026, 56.6%), obesity (1737, 41.7%), and diabetes (1808, 33.8%) appeared to be the most common medical problems that were associated with COVID 19 infection and might predict severity of the disease.(29) Recently, one study from United States of America, assessed the comorbidities during this COVID 19 pandemic among pregnant women. Obesity was the most common associated comorbidity (60.5%) and (41.8%) had an additional comorbid condition, including mild intermittent bronchial asthma (18.6%), type 2 diabetes mellitus (7.0%) and chronic hypertension (7.0%).(30) Obese and obese-diabetic state are characterized by

chronic and low-grade inflammation that affects different steps of the innate and adaptive immune response.(31) Furthermore, chronically higher leptin (a pro-inflammatory adipokine) and lower adiponectin (an anti-inflammatory adipokine) concentrations were observed among obese subjects. (32) Similarly, Reduced physical activity and insulin resistance hinder immune response against microbial agents .(33,34) Additionally, obese patients are more likely to delay clearance of influenza virus and vulnerable to the emergence of novel and more virulent virus strains as a result of impaired interferons production (35,36). Likewise, people with asthma are more likely to have severe outcomes with common cold virus infections than those without it (37), and dramatically worsening is observed in uncontrolled asthma as a result of virus-induced exacerbation.(38) Deficient and delayed innate anti-viral immune responses, besides observed deficiency and delay in lung cell cytokines functions (interferon (IFN)- α (39), IFN- β (40) and IFN- λ (41)) in patients with bronchial asthma.(41) Furthermore, the deficiency of IFN- λ is causally linked to increased asthma exacerbation episodes and severity.(41) Based on this evidence, may deduce that bronchial asthma should be considered as a risk factor and predictor for severe outcomes in COVID-19 disease. Additionally, in the largest case series recruiting 44,672 confirmed COVID-19 cases, reported chronic respiratory disease, including bronchial asthma, as the third highest case fatality ratio, after cardiovascular disease and DM.(43) Common comorbidities, DM (7.4%) and hypertension (15.0%) were frequently reported in patients with confirmed COVID-19 and predicted the severity of the disease.(11) Similar outcome was obtained regarding the higher rate of comorbidities among infected cases with COVID-19 as they were more vulnerable than the general population (44,45) predicts hospital admission(46) and intensive care management.(44) Recently, one study pointed to the associated comorbidities (hypertension, proteinuria, gestational diabetes mellitus and morbid obesity) and the risk developing pulmonary edema/embolism, from COVID-19 infection during pregnancy. (47) Hence, pregnancy might mask the beneficial effect of the gender as cellular studies revealed attenuation of Angiotensin-converting enzyme 2 expression in females, that supporting the

epidemiological observation of male predominance for susceptibility of COVID-19 infections. (11,48) Based on these evidences, coexistence of comorbidities during pregnancy appears to be an additive risk factor for susceptibility and predictor for severe COVID 19 infection that necessitates proper management to achieve a favorable prognosis.

Pregnancy is considered as a partially immunocompromised state, hence pregnant women are more susceptible to viral or bacterial pneumonia than non-pregnant adults, leading to life-threatening condition during pregnancy.(49) Since SARS-CoV-2 is a novel virus, thus herd immunity is not well developed yet among individuals that, makes everyone susceptible.(50) Likewise, pregnant women are more vulnerable to respiratory pathogens including COVID-19 infection than the general population.(50) The effects of elevated level progesterone and estrogen during pregnancy in promoting Th2-type immune responses favoring adaptive immune response to maintain progression of the pregnancy, was identified in some clinical data(20,21) besides, the influence of prolactin in innate immunity. (22) This might explain the relative improvement or reduce severity during pregnancy for some T helper cell type 1-mediated autoimmune diseases (rheumatoid arthritis and multiple sclerosis), and T helper cell type 2-mediated disorders such as systemic lupus erythematosus.(20-22) T-helper lymphocytes are the major cytokines producers that regulate immune response and inflammatory process. Th1-type cytokines are basically microbicidal and proinflammatory properties which include interferon-g (IFN-g), interleukin (IL)1a, IL-1b, IL-6, and IL-12.(51) This is usually balanced naturally by Th2-type cytokines which work as anti-inflammatory substances and comprise IL-4, IL-10, IL-13, and transforming growth factor b.(51) During pregnancy, the bias toward Th2 system dominance and the attenuation in cell-mediated immunity by Th1 cells due to the physiological shift, that favoring fetus protection, leaving the mother vulnerable to the risk of viral infections and other intracellular pathogens.(52) These unique challenges play a potential role in increasing susceptibility to viral infections including SARS-CoV-2.(52) Given that the cytokine profiles in SARS-CoV and SARS-CoV-2 infections in nonpregnant

patients, may be extrapolated to account for the differences in disease severity during pregnancy.(53) In fact patients with SARS disease showed preferential activation of Th1 immunity, which is characterized by marked elevation of proinflammatory cytokines (IFN γ , IL-1 β , IL-6, and IL-12), leading to extensive lung damage and complicates disease presentation.(54) On the other hand, patients with COVID-19 disease, have tendency to activate both Th1 and Th2 immune response during the course of the disease.(55) In addition, elevated levels of IL-6, a predominant Th1 cytokine, are associated with a significantly increased risk of mortality in patients with COVID-19 disease.(56) In murine experimental studies of influenza, have documented that pregnancy potentiates influenza-related pathology as a result of defective viral clearance, increased pulmonary cytokines (IL6, IL-1 α), and Granulocyte-colony stimulating factor expression. Moreover, prostaglandin and progesterone levels have influential role in immune response during pregnancy. (57) The study extrapolated that immunological responses to viral pathogens are influence by the hormonal changes during pregnancy. (57) Hence early adaptive immune responses during COVID 19 infection may predict severity of the disease.(58) In contrast, one study justified the lesser severity of COVID-19 infection among pregnant women compared to that in nonpregnant individuals, due to the physiological transition to a Th2 activities, favoring the arm of anti-inflammatory cytokines (IL-4 and IL-10) and other possible unknown immune adaptations.(59) Additionally, lymphocytopenia was reported in considerable number of COVID 19 cases during pregnancy (59%) and associated with an elevated C-reactive protein concentration (>10 mg/L) in (70%) of cases.(8) Moreover, the Innate immune cells, such as Natural killer cells and monocytes, are in particular, protecting the body from viral invasion.(60) This mission is markedly modulated during pregnancy by the adaptive immune responses: down-regulated during pregnancy (decreased numbers of T and B cells) hence hindering its antiviral efficacy.(60) Severe COVID-19 infection is related to cytokine-storm, which is characterized by increased plasma concentrations of different cytokines: interleukins 2 (IL2), IL-7, IL-10, tumor necrosis factor α (TNF- α), interferon- γ -inducible protein 10, granulocyte-colony

stimulating factor, monocyte chemoattractant protein 1 and macrophage inflammatory protein 1 alpha.(55) Basically, it is triggered by antibody dependent enhancement of SARS-CoV-2 as a result of prior exposure to similar antigenic epitopes with other members of coronaviruses family.(61) Hence, the characteristic immune responses during pregnancy and potential risks of COVID-19 infection induced cytokine-storm have severe morbidity and predict mortality(50). Not only pregnant women may be affected during cytokine storm, but fetus may suffer from several associated complications: fetal brain development with a wide range of neuronal dysfunctions and behavioral phenotypes.(62) On the other hand, some studies considered pregnant women are not more susceptible to the majority of infectious diseases, nor they are immune from effects of the majority of autoimmune disorders. (20-22) Similarly, some authors preferred to refer to pregnancy as a unique immune state that is modulated, but not suppressed. (21,22,63)

Pregnancy is physiologically hypercoagulable state, with rising levels of coagulation factors as reflected by 50% increase in fibrinogen and D-dimers above baseline by the third trimester.(64) The dysfunction of endothelial cells induced by infection results in excess thrombin generation and fibrinolysis shutdown, which indicated a hypercoagulable state in patient with infection,(65- 68) such as COVID-19 infection that resulted in diffuse endothelial inflammation.(69) In addition, the hypoxia found in severe COVID-19 can stimulate thrombosis through increasing blood viscosity and a hypoxia-inducible transcription factor-dependent signaling pathway.(70-72) As an evidence, occlusion and micro-thrombosis formation in small pulmonary vessels of critical patient with COVID-19, has been reported from a recent lung tissue study.(73) Hence, early initiation of anticoagulant therapy in severe COVID-19 disease was recommended to improve the outcome.(74) It was clearly documented in case series study, disseminated intravascular coagulopathy (DIC) complicated COVID19 infection in pregnant women.(16) Likewise, the observation of higher D-dimers levels in non-survivors when was compared to survivors of COVID 19 infection.(71) While, previous study, was not promoting the use typical D-dimer rise during gestation as indicator for

unfavorable prognosis in pregnancy(64), recent study, justified a significant D-dimer elevation (cutoff; 3-4fold above ULN) as clear indication for hospital admission irrespective of absence of other suggestive symptoms.(75) Furthermore, severe pneumonia causally related to COVID 19 is frequently associated with coagulopathy and a high level of D- dimer and is directly linked to poor prognosis.(55,71,76) In the light of unvalidated sepsis induced coagulopathy (SIC) score during pregnancy, the poor prognostic implication of high D-dimers and beneficial effects of anticoagulation prophylaxis therapy in non-pregnant individuals with COVID19 infection, prophylactic low-molecular-weight heparin administration may be of paramount value when immediately use in the postpartum period for COVID 19 positive cases.(77) This was strengthened by recent study that assessed the DIC, based on the International Society on Thrombosis and Hemostasis (ISTH) criteria among survivors and non-survivors of COVID-19 infection, which were 0.6% and 71% respectively. (78) Increased mortality was observed with high levels of APTT, PT, D-dimer, and fibrin degradation products compared to COVID19 survivors.(71) Surprisingly, neither APTT nor low fibrinogen was evaluated in a pregnancy series although both being used as elements in DIC classification.(77) On the other hand, data related to other tests lacks strong certainty and often conflicting (79,80) Plausibly there is documented observation that linked maternal COVID19 infection in third-trimester and rapid maternal deterioration, with progressive coagulopathy and confirmed recovery shortly after delivery.(77) Hence, COVID 19 infection during pregnancy may presage impending risk of serious complications and may explain the higher rate of caesarean sections during the third trimester of pregnancy to hasten delivery.(8) It is worth to mention that the evidences link the prevalence and genetic risk factors of venous thromboembolism, vary significantly among different ethnic populations as low incidence of venous thromboembolism event was observed in Asian compared to Western population.(81-83) Recently, some published data pointed to the association of severe coronavirus disease 2019 (COVID-19) and complicated coagulopathy, DIC and the majority of deaths.(55,71,76) The ISTH has proposed a new category identifying an earlier phase of sepsis-

associated DIC called “sepsis-induced coagulopathy” (SIC).(84) that will help to take decision for initiating anticoagulant therapy based on the diagnostic criteria of SIC.(85)

In fact, chronic neutropenia which is relatively immunocompromised state that related to the COVID19 course, is not a known cause of pregnancy associated coagulopathy.(77) This goes with the finding of a retrospective cohort study recruiting 38 pregnant women with chronic neutropenia syndromes, revealed no single case of coagulopathy was reported.(86) Hence, they extrapolated that the immunocompromised state causally related to the COVID19 infection. (77) Likewise, COVID-19 infection is commonly associated with lymphopenia,(87) elevated lactate dehydrogenase and higher levels of inflammatory markers (D-dimer, ferritin, C reactive protein, and interleukin-6 (IL-6)).(88) Moreover, elevated IL-6 levels may predict disease severity, and correlate with a procoagulant profile.(89) Basically, the most consistent hemostatic abnormalities with COVID-19 infection are mild thrombocytopenia,(80) and elevated D-dimer levels,(90) which hire a higher risk of severe morbidity and increased fatality: increase rate of mechanical ventilation, intensive care unit admission, or death.(79,80) Surprisingly, patients with severe pneumonia induced by SARS-CoV2 had higher platelet count than those induced by non-SARS- CoV2infection, but only the former with significant higher levels of D-dimer may gain benefit from anticoagulant therapy.(55,71,76,91) This might indicate the severe inflammatory reaction and hypercoagulability among patients with COVID infection, and platelet count is not a sensitive marker for coagulopathy process related to COVID-19 disease.(55,71,76,91)

It is important to consider the side effects of some medications that are used for treating COVID-19 infection and have interactions with oral antiplatelet agents and increase risk of coagulopathy: Lopinavir/ritonavir is a protease inhibitor and inhibits CYP3A4 metabolism, ticagrelor inhibits CYP3A4 that potentiates its effects and remdesivir, a nucleotide-analog inhibitor of RNA-dependent RNA polymerase, is an inducer of CYP3A4.(78) Clinically, incident venous thromboembolism was reported in 25% of severe COVID 19 patients who required ICU admission in

china,(92) 30% in the Netherlands,(93) and 40% diagnosed with pulmonary embolism based computed tomography angiography imaging.(94) Furthermore, a retrospective study from China, revealed 5% incidence of stroke among hospitalized patients with Covid-19.(95) Pregnancy, COVID 19 infection and some medications used during the course of the disease are collectively increase the risk of susceptibility and severity of coagulopathy events.

Conclusion; -

Pregnancy, associated comorbidities and adaptive immune response are potential risk factors for contracting COVID 19 and predict maternal and perinatal complications. Moreover, pregnancy and COVID 19 infection, directly and indirectly magnify the risk of coagulopathy, hence vigilant and proper management are warranted for such patients.

Limitation

This study used only Pubmed and Google scholar database and some valuable data are not included. Lack of data assessing large number of pregnant women as it is novel virus. Other risk factors like age, other comorbidities, maternal and perinatal are not covered here. Another limitation is related to the article selection criteria that were used.

Abbreviations

COVID 19; Coronavirus disease 2019

SARS-CoV; Severe acute respiratory syndrome coronavirus.

MERS-CoV; Middle East respiratory syndrome coronavirus.

DM; Diabetes mellitus.

ICU; Intensive Care Unit.

IFN- γ ; Interferon gamma.

TNF- α ; Tumor necrosis factor alpha.

IL; Interleukin.

CD8+ T cells; CD8+ (cytotoxic) T cells.

Th1 ; T helper cell type1.

Th2 ; T helper cell type 2.

ISTH; International Society on Thrombosis and Haemostasis.

DIC; Disseminated intravascular coagulopathy.

SIC ; Sepsis induced coagulopathy.

Authors' contributions

IR designed the study, gathered and entered the data, drafted the manuscript, revised the manuscript and finalized it.

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None.

Competing interests

I have no competing interests.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the database search engine.

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