Orijinal Araştırma / Original Investigation
Aegean J Med Sci 2023;1:1 -6

A Mortality Prediction Model in Pregnant and Postpartum Women With Covid-19 Admitted to the Intensive Care Unit

Yoğun Bakım Ünitesinde yatan Covid-19'lu Gebe ve Lohusaların Mortalite Risk Faktörleri

İsa Kılıç[1], Gültekin Adanaş Aydın[2], Hilal Gülsüm Turan Özsoy[3], Serhat Ünal[2]

1 Department of Anesthesiology and Reanimation, Intensive Care Unit, Bursa City Hospital, Bursa/Turkey
2 Department of Obstetrics and Gynecology, Bursa City Hospital, Bursa/Turkey
3 Department of Radiology, Bursa City Hospital, Bursa/Turkey

ÖZET

AMAÇ: Bu çalışmada yoğun bakımda yatan COVID-19 tanılı gebe ve lohusalarda mortalite prediksiyon modeli oluşturarak APACHE II, SAPS II ve SOFA skorları ile karşılaştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM: Hastanemizin COVID-19 yoğun bakım ünitelerine yatan Covid-19 tanısı doğrulanmış gebe ve lohusaların demografik, laboratuvar, radyolojik ve klinik verileri geriye dönük olarak kaydedildi.

BULGULAR: Çalışmaya dâhil edilen 50 hastadan 13'ü kaybedildi. Yaş ortalaması ölen grupta 35.54±4.24 yıl, yaşayan grupta 30.03±4.91 yıl idi (p=0,002). Lojistik regresyon modeli, yaş, lenfopeni, yüksek CRP ve IL-6 düzeylerinin mortalite ile ilişkili olduğunu ortaya koydu. Modelin mortalite (AUC) için prediktif gücü 0.946±0.045 (p<0,001) idi. ROC eğrisi altında kalan alan (AUC) APACHE II skoru için 0.712±0.085 (p=0.024), SAPS II skoru için 0.481±0.102 (p=0.842) ve SOFA skoru için 0,656±0,089 (p=0,097) idi. Modelimizin özgüllüğü %97,3, duyarlılığı %84,6, prediktif değeri %91,7 ve negatif prediktif değeri %94,7 idi.

SONUÇ: Oluşturduğumuz tahmin modeli klinisyene, yoğun bakım ünitesine kabul edilen COVID-19 tanılı gebe ve lohusalarda yüksek mortalite riski olan vakaların belirlenmesine olanak tanıyacaktır.

Anahtar Kelimeler: Covid-19, mortalite, gebe, SARS-CoV-2, lenfopeni, yoğun bakım

ABSTRACT

OBJECTIVE: In this study, it was aimed to compare with APACHE II, SAPS II and SOFA scores by creating a mortality prediction model in pregnant and postpartum women with a diagnosis of COVID-19 in intensive care (ICU).

MATERIALS AND METHODS: Demographic, laboratory, radiological and clinical data of pregnant and postpartum women with confirmed COVID-19 diagnosis who were admitted to the COVID-19 ICUs of our hospital were recorded retrospectively.

RESULTS: Of the 50 patients included in the study, 13 died. The mean age was 35.54±4.24 years in the non-surviving group and 30.03±4.91 years in the surviving group (p=0.002). A logistic regression model revealed age, lymphopenia, elevated CRP and IL-6 levels to be associated with mortality. The predictive power of the model for mortality (AUC) was 0.946±0.045 (p<0.001). The area under an ROC curve (AUC) was 0.712±0.085 for the APACHE II score (p=0.024), 0.481±0.102 (p=0.842) for the SAPS II score and 0.656±0.089 for the SOFA score (p=0.097). Our model had a specificity of 97.3%, a sensitivity of 84.6%, a predictive value of 91.7%, and a negative predictive value of 94.7%.

CONCLUSION: The prediction model we created will allow the clinician to identify cases with a high risk of mortality risk in pregnant and postpartum women with a diagnosis of COVID-19 admitted to the ICU.

Keywords: Covid-19, mortality, pregnant women, SARS CoV-2, lymphopenia, critical care

INTRODUCTION

The threat to human life of Coronavirus disease 2019 (COVID-19) first arose in December 2019. According to data of the World Health Organization (WHO), by April 3, 2022 there had been over 489 million recorded cases of COVID-19 and more than 6 million deaths reported globally (1). Pregnancy predisposes women to respiratory viruses and the complications of infections caused by such viruses, and infections caused by respiratory viruses are more severe in pregnant women due to the changes that occur in the anatomical, cardiopulmonary and immune systems (2,3,4). Admission to the intensive care unit (ICU), the need for invasive mechanical ventilation (IMV) and mortality are

Yazışma Adresi/Address for Correspondence: İsa Kılıç, MD, Konak Mahallesi Yasemin Sokak Maverapark Apartmanı A Blok Daire: 9, Nilüfer / Bursa, Turkey
E-Posta/E-Mail: kilicisaicu@gmail.com ‖ **Tel:** +90 5053513825
Received/Geliş Tarihi: 26.08.2022 ‖ **Accepted/Kabul Tarihi:** 18.01.2023

more common in pregnant women with COVID-19 when compared to non-pregnant women of reproductive age (5).
The early accurate assessment of severe COVID-19 patients may contribute to the initiation of the necessary treatments and the reduction of mortality (6). Models that have been developed based on combinations of different variables and characteristics for the prediction of potential adverse outcomes of infection in pregnant women support the planning and prioritization of patients and the allocation of healthcare resources. To the best of our knowledge, however, there is yet no specific scoring system in literature for the determination of mortality in pregnant and postpartum women with COVID-19 admitted to the ICU. Furthermore, there have been few studies conducted using such scoring systems as the Acute Physiology and Chronic Health Evaluation (APACHE) II, the Simplified Acute Physiology Score (SAPS) II and the Sequential Organ Failure Assessment (SOFA) to predict mortality in adult COVID-19 patients admitted to the ICU (7,8), although there are ongoing discussions about the ability of the APACHE II score to predict ICU mortality in patients with COVID-19 (9).
We present here a model that has been developed for the identification of the risk factors associated with mortality, and for the prediction of ICU mortality in pregnant and postpartum women with severe COVID-19. As a further purpose of the study, we make a retrospective assessment of the value of SOFA, SAPS II and APACHE II scores for the prediction of mortality in patients, and compare these scores with those of our model.

MATERIAL & METHODS

This single-center retrospective observational study was conducted with pregnant and postpartum women patients over 18 years of age with COVID-19 confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) between April 2020 and December 2021 in the Level-3 ICUs of Bursa City Hospital. The study protocol was approved by TC University of Health Sciences; Bursa School of Medicine; Bursa City Hospital Ethics Committee (Date: 09.03.2022; Decision No: 2022-3/10) and the study was conducted following the principles of the Declaration of Helsinki. Since our study was retrospective, informed consent was not obtained from the patients.

The study data were obtained from the electronic health records of our hospital. Excluded from the study were pregnant and postpartum women with critical illnesses at the time of diagnosis, those younger than 18 years of age, those with a negative RT-PCR test result for SARS-CoV-2, and those with previous COVID-19 disease. All patients were managed in accordance with the Ministry of Health Diagnosis and Treatment Guidelines.

The reasons for admission to the ICU (respiratory failure, organ failure, hemodynamic instability, eclampsia, etc.) were recorded, along with age and body mass index (BMI) at the time of admission, comorbidities, smoking habits, history of medication, gestational age at admission, gravidity, and parity, variant of SARS-CoV-2, COVID-19 vaccination status, laboratory values (WBC (white blood cells, platelets), ferritin, fibrinogen, lymphocytes, D-dimer, CRP (C-reactive protein), procalcitonin, LDH (lactate dehydrogenase), ALT (alanine aminotransferase), AST (aspartate aminotransferase), INR (international normalized ratio), aPTT (activated partial thromboplastin time), PT (prothrombin time), SpO2 (oxygen saturation), PaO2 (partial arterial oxygen pressure), PaO2/FiO2 (partial arterial oxygen pressure/fraction of inspired oxygen) ratios, and APACHE II, SAPS II, and SOFA scores. Medical treatments (Remdesivir, Plaquenil, steroids, favipiravir, anakinra, tocilizumab, cytokine filter, plasmapheresis/IVIG, anticoagulation), treatments for respiratory failure (IMV, high-flow oxygen therapy (HFOT), non-invasive mechanical ventilation (NIMV), oxygenation mask), and the duration of the patients' stays in the hospital and the ICU were recorded.

Thoracic computed tomography (CT) scans and chest radiographs were evaluated on the Picture Archiving and Communication System (PACS). All thoracic CT scans and chest radiographs were reviewed by a radiologist with more than 10 years of experience in thoracic radiology. Pneumonia was classified as mild, moderate, and severe pneumonia based on radiological imaging, and the classification was made using the Radiographic Assessment of Lung Edema (RALE) Scoring System on chest radiographs (10).

Thoracic CTs were grouped based on the patient's chest CT Score (11). Accordingly, both lungs were divided into five lobes and each lobe was assessed individually.

The APACHE II score was calculated using respiratory rate, arterial pH, PaO2, temperature, age, heart rate, mean arterial pressure, levels of sodium (Na+), potassium (K+),

creatinine (Cr), and hematocrit, leukocyte count, Glasgow Coma Scale (GCS), and previous health status (surgery, history of organ failure, immunocompromised status) data. The SAPS II score was calculated using leukocyte count, bilirubin, bicarbonate, Na+ and K+ levels, heart rate, systolic blood pressure, age, body temperature, GCS, PaO2/FiO2 ratio, mechanical ventilation or continuous positive airway pressure, urine output, urea, chronic diseases, and type of admission data. The SOFA score was calculated based on respiratory (PaO2/FiO2) cardiovascular (vasoactive agent requirement), hepatic (bilirubin level), coagulation (platelet count), neurological (GCS), and renal system (serum creatinine and urine output) disorders. All scores were calculated using the worst values of the parameters within the first 24 hours of admission (12).

The patients were divided into two groups as those who survived and those who died in the ICU (survivors and non-survivors). The mortality risk factors for the two groups were determined and a mortality prediction model was developed, after which, the performance and validity of ICU mortality prediction scores in patients were assessed.

Descriptive statistics of the study data were calculated as means, standard deviation (SD), counts and % frequencies. A Shapiro-Wilk test was used to analyze the normality of the quantitative data. The unadjusted effects of quantitative characteristics alone were established through a comparison of the surviving and non-surviving pregnant women with COVID-19 using a Mann-Whitney U test. Likewise, the unadjusted effects of categorical characteristics on mortality were established with a Pearson's Chi-square test. Variables with significant ($p <= 0.10$) unadjusted effects on mortality in the univariate tests were included in the binary logistic regression model. The variables that would remain in the final model were identified using a stepwise variable elimination method. Missing data were estimated using the simple tree method prior to the building of the model. Statistical significance was set at $p <= 0.10$ for unadjusted effects and $p <= 0.05$ for adjusted effects. Calculations were made using IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 50 pregnant and postpartum women with COVID-19 who were admitted to the ICU were included in the study. Of the total, 13 of the pregnant women died and the rest were eventually discharged.

The mean age was 35.54±4.24 years and the mean BMI was 29.06±5.54 in the non-surviving group, while the mean age and BMI were 30.03±4.91 years and 27.59±4.33, respectively, in the surviving group (p=0.002 and p=0.446).

Considering the demographic characteristics, and laboratory and radiological findings, the mean LDH, CRP, aPTT, IL-6 and FiO2 were statistically significantly higher in the non-surviving patient group than in the surviving group (p=0.020, p=0.001, p=0.066, p=0.002, and p=0.008), while the mean lymphocyte count, PaO2 and PaO2/FiO2 were significantly lower (p=0.025, p=0.035, and p= 0.003) (Table 1).

A comparison of the radiology results of the two groups revealed a significantly higher mortality rate in pregnant and postpartum women with severe involvement than in the mild and moderate categories (p=0.1). Moreover, the rate of mortality was significantly higher in those who were intubated (p=0.001) and unvaccinated (p=0.036), in those who did not receive mask oxygen (p=0.065), and in those who received IMV (p=0.001), HFOT (p=0.05), NIMV (p=0.001), antibiotics (p=0.12), pulse steroids (p=0.007), steroids (p=0.067), anakinra (0.043) and favipiravir (p=0.091). Aside from this, no significant difference between the two groups was identified (Table 2).

The variables with statistical significance or a p-value close to statistical significance ($p < 0.10$) in Tables 1 and 2 were included in the logistic regression model, thereby revealing the adjusted effects of the risk factors with a significant effect on mortality. Ventilation and intubation, however, were not included in the model, being risk factors that emerge in the final status of the patients, and the primary purpose of the model was to predict mortality based on early-period markers.

The model results are summarized in the nomogram presented in Figure 1, and reveal the risk factors that significantly affect mortality to be age and the lymphocyte, CRP, and IL-6 levels in the ICU.

Considering the performance measures of the model, the area under the ROC curve (AUC) was 0.946±0.045, suggesting that the model had good performance in discriminating between non-survivors and survivors ($p<0.001$, Figure 2). Moreover, when the diagnostic success of the scores used in the ICU was examined, AUC was found

to be 0.712±0.085 for APACHE II (p=0.024), 0.481±0.102 for SAPS II (p=0.842), and 0.656±0.089 for SOFA (p=0.097).

The predictive success (specificity) of the logistic regression model was 91.9 % and the success (sensitivity) in discriminating non-survivors was 61.5 %. In addition, the positive and negative predictive values of the model were 72.7 % and 87.2 %, respectively. The overall accuracy of the model was 84%. Based on these results, the model performance can be concluded to be quite good (Table 3).

When the success of the APACHE II, SOFA, and SAPS II scores in the discrimination of non-survivors were examined individually, only the mean APACHE II and SOFA scores were found to be significantly higher in non-surviving patients, meaning that these two scores were able to successfully discriminate non-survivors. The SAPS II score, on the other hand, could not significantly discriminate between non-survivors and survivors (Table 4). The success of these three scores in discriminating non-survivors is presented graphically in Figure 2 with a ROC curve.

DISCUSSION

A high-performance model and normogram were developed in the present study for the prediction of mortality based on laboratory data, imaging data, demographic characteristics and comorbidities at the time of the ICU admission of pregnant and postpartum women with COVID-19 confirmed by RT-PCR for SARS-CoV-2. The model identified elevated CRP and IL-6 levels, advanced age and lymphopenia as independent risk factors in pregnant and postpartum women with COVID-19 admitted to the ICU. We also assessed the performance of SAPS II, APACHE II and SOFA scores for the prediction of ICU mortality in this patient group, and found the SAPS II score not to be significant in predicting mortality in our patient group (performance measure; AUC: 0.481±0.102), and the performance of our model (AUC: 0.946±0.045) to be superior to that of the APACHE II (AUC: 0.712±0.085) and SOFA scores (AUC: 0.656±0.089, p=0.097).

In adult intensive care patients, the APACHE II, SAPS II and SOFA scores are commonly used to predict mortality, the severity and prognosis of disease, and intensive care performance. In a study of ICU patients with COVID-19, Zou et al. assessed the relationship between APACHE II score and mortality, and compared the predictive powers of APACHE II and SOFA scores in patients, and reported the APACHE II and SOFA scores to be significant in predicting mortality (33.77%) (10.87±4.47 vs. 23.23±6.05; p<0.001). The authors reported further that the APACHE II score (AUC: 0.966) had a higher predictive power for mortality than the SOFA score (AUC: 0.867).7 Similar to the study by Zou et al., another study, involving 52 ICU patients, found a median APACHE II score of 18 and a mortality rate of 61.5% in non-surviving patients (13).

The median APACHE II score in the present study was 9.62 and the mortality rate was 26% in the non-survivors, which is lower than that reported in previous studies. The APACHE II and SAPS II scores in both our study and in other studies were surprisingly low when compared to mortality rates. The APACHE II and SAPS II scores are calculated based on the worst values within the first 24 hours of admission. Biomarkers identifying disease severity may arise in a later period in COVID-19 patients with respiratory failure at admission, and therefore will have no effect on these scores. Despite the statistically significant APACHE II score in other studies and our study, we believe that it does not reflect the actual mortality.

Clinical presentations of COVID-19 may range from mild symptoms to cytokine storm and multi-organ failure. The cytokine storm induced by COVID-19 is associated with an increase in various cytokines, such as serum TNF, IL-1B and IL-6 (14). In addition to its proinflammatory effects, IL-6 activates many acute phase reactants and the coagulation cascade (15). IL-6 has been shown to be an independent risk factor for mortality, and mortality to be associated with high IL-6 levels (15,16). A previous meta-analysis reported that IL-6 antagonists reduced the 28-day mortality and duration of IMV in critical COVID-19 patients when compared to the usual treatment and placebo (17), and we also identified elevated IL-6 level as an independent risk factor for mortality in the present study.

The excessive inflammation and immunosuppression caused by SARS-CoV-2 infection result in a progressive decrease in the lymphocyte count in severe COVID-19 cases (18). In other words, the systemic inflammation induced by SARS-CoV-2 suppresses cellular immunity, leading to a decrease in CD3+T, CD4+T, and CD8+T cell counts (19). A previous study reported WBC counts to be normal or low and lymphopenia to be common in COVID-19 patients, and associated a lymphocyte count of <1000 with severe COVID-

19 (20). Yet another study reported lymphopenia to be common in COVID-19 patients, while the white blood cell count varied. The same study reported severe lymphopenia to be associated with critical illness and mortality (21). In another meta-analysis, it was found that severe lymphopenia was associated with mortality in adult intensive care patients with a diagnosis of Covid 19 (22). Lymphopenia was also identified as an independent risk factor for mortality in the present study.

It should be kept in mind that inflammatory markers such as CRP may increase slightly during normal pregnancy (23). Kalafat et al. (24) developed two different prediction models to evaluate maternal mortality, progression to severe Covid 19, and admission to the ICU in an international and multicenter study conducted in 793 pregnant and postpartum women with symptomatic Covid 19. In the fullCOMIT model, which is one of the models they developed, they showed that high CRP was an independent risk factor effective for maternal mortality. Yao et al. developed a prediction model for the early detection of clinical deterioration in pregnant women with COVID-19, identifying CRP levels of >2.0 mg/dL as a risk factor (25). Another study of adult COVID-19 patients reported CRP (normal range: <8.0 mg/L) levels of >100 mg/L to be a risk factor for adverse outcomes (26). In another study involving adult patients, Ruan et al. showed elevated CRP in COVID-19 patients to be a risk factor for mortality (16), and we also found elevated CRP to be a risk factor for mortality in the present study. There is currently no reference level related to CRP and COVID-19 infection in pregnancy in literature (23).

Another risk factor that we found to be significant in our model was age. A meta-analysis of pregnant women with COVID-19 reported advanced maternal age to be associated with severe COVID-19 and ICU admission (5), and a number of observational studies concur, identifying advanced age as an independent risk factor for mortality in COVID-19 patients (24,26-28). We also identified advanced age as an independent risk factor for mortality in our study.

The main limitation of our study is its retrospective design. To the best of our knowledge, our study is the first to develop a prediction model for the prediction of ICU mortality in pregnant and postpartum women with COVID-19. The strength of our study is the administration of the same treatment protocol to all patients.

CONCLUSION

We developed a risk model with reasonably high performance in predicting mortality in pregnant and postpartum women admitted to the ICU due to COVID-19. We found this model to be superior to other scoring systems for the determination of ICU mortality. The identified risk factors are laboratory parameters that can be studied in many centers and risk factors such as age, and thus the model allows the clinician to identify cases with a high risk of mortality among pregnant and postpartum women with COVID-19 admitted to the ICU as a specific patient group.

Etik: Bu çalışmanın etik kurulu alınmıştır.

Ethics committee approval had been taken.

Yazar katkı durumu; Çalışmanın konsepti; İK, GAA, HGTÖ, SÜ, dizaynı; İK, GAA, HGTÖ, SÜ, Literatür taraması; İK, GAA, HGTÖ, SÜ, verilerin toplanması ve işlenmesi; İK, GAA, HGTÖ, SÜ, istatistik; İK, GAA, HGTÖ, SÜ, yazım aşaması; İK, GAA, HGTÖ, SÜ.

Author contribution status; The concept of the study; İK, GAA, HGTÖ, SÜ, design; İK, GAA, HGTÖ, SÜ, literature review; İK, GAA, HGTÖ, SÜ, collecting and processing data; İK, GAA, HGTÖ, SÜ, statistics; İK, GAA, HGTÖ, SÜ, writing phase; İK, GAA, HGTÖ, SÜ.

Yazarlar arasında çıkar çatışması yoktur.

The author declares no conflict of interest.

Finansal Destek: yoktur / Funding: none

doi: https://doi.org/10.33713/egetbd.1167278

REFERENCES

1. WHO Coronavirus (COVİD-19) Dashboard. (https://www.who.int/);[Accessed 03 April 2022].

2. Poon LC, Yang H, Dumont S, Lee JCS, Copel JA, Danneels L, et al. ISUOG Interim Guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium: information for healthcare professionals - an update. Ultrasound Obstet Gynecol 2020;55(6):848-62.

3. Yanes-Lane M, Winters N, Fregonese F, Bastos M, Perlman-Arrow S, Campbell JR, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. PLoS One 2020 3;15(11):e0241536.

4. Karasu D, Kilicarslan N, Ozgunay SE, Gurbuz H. Our

anesthesia experiences in COVID-19 positive patients delivering by cesarean section: A retrospective single-center cohort study. J Obstet Gynaecol Res. 2021 Aug;47(8):2659-2665

5. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020; 1;370:m3320.

6. Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Am J Emerg Med. 2020;38(10):2074-80.

7. Zou X, Li S, Fang M, Hu M, Bian Y, Ling J, et al. Acute physiology and chronic health evaluation II score as a predictor of hospital mortality in patients of coronavirus disease 2019. Crit Care Med 2020;48(8):e657-e665.

8. Wilfong EM, Lovly CM, Gillaspie EA, Huang LC, Shyr Y, Casey JD, et al. Severity of illness scores at presentation predict ICU admission and mortality in COVID-19. J Emerg Crit Care Med. 2021;5:7.

9. Stephens JR, Stümpfle R, Patel P, Brett S, Broomhead R, Baharlo B, et al. Analysis of critical care severity of illness scoring systems in patients with coronavirus disease 2019: A retrospective analysis of three U.K. ICUs. Crit Care Med 2021;49(1):e105-e107.

10. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and distribution of chest radiographic findings in patients positive for COVID-19. Radiology 2020;296(2):E72-E78.

11. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol 2020;55(6):327-31.

12. Godinjak A, Iglica A, Rama A, Tančica I, Jusufović S, Ajanović A, et al. Predictive value of SAPS II and APACHE II scoring systems for patient outcome in a medical intensive care unit. Acta Med Acad 2016;45(2):97-103.

13. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. 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 2020;8(5):475-81.

14. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383(23):2255-73.

15. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis 2020;95:332-39.

16. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46(5):846-48.

17. Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, Spiga F, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: A Meta-analysis. JAMA 2021;326(6):499-18.

18. Mangalmurti N, Hunter CA. Cytokine storms: Understanding COVID-19. Immunity 2020;53(1):19-25.

19. Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020;75(7):1564-81.

20. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 2020;87(4):281-86.

21. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-513.

22. Taylor EH, Marson EJ, Elhadi M, Macleod KDM, Yu YC, Davids R, et al. Factors associated with mortality in patients with COVID-19 admitted to intensive care: a systematic review and meta-analysis. Anaesthesia 2021;76(9):1224-32.

23. Vega M, Hughes F, Bernstein PS, Goffman D, Sheen JJ, Aubey JJ, et al. From the trenches: inpatient management of coronavirus disease 2019 in pregnancy. Am J Obstet Gynecol MFM 2020;2(3):100154.

24. Kalafat E, Prasad S, Birol P, Tekin AB, Kunt A, Di Fabrizio C, at al. An internally validated prediction model for critical COVID-19 infection and intensive care unit admission in symptomatic pregnant women. Am J Obstet Gynecol. 2022;226(3):403.e1-403.e13.

25. Yao R, Martin CB, Haase VS, Tse BC, Nishino M, Gheorghe C, et al. Initial clinical characteristics of gravid severe acute respiratory syndrome coronavirus 2-positive patients and the risk of progression to severe coronavirus disease 2019. Am J Obstet Gynecol MFM 2021;3(4):100365.

26. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 2020;26(10):1636-43.

27. African COVID-19 Critical Care Outcomes Study (ACCCOS) Investigators. Patient care and clinical outcomes for patients with COVID-19 infection admitted to African high-care or intensive care units (ACCCOS): a multicentre, prospective, observational cohort study. Lancet 2021;397(10288):1885-94.

28. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021;47(1):60-73.