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Initial clinical characteristics of gravid severe acute respiratory syndrome coronavirus 2—positive patients and the risk of progression to severe coronavirus disease 2019

Ruohan Yao, MD, MPH; Courtney B. Martin, DO; Victoria S. Haase, MD; Beverly C. Tse, MD; Melissa Nishino, BS; Ciprian Gheorghe, MD, PhD; Kevin Balli, MD

BACKGROUND: Available data suggest that the obstetric population is particularly vulnerable to severe respiratory syndrome coronavirus 2 infection, with a variable clinical course leading to severe respiratory failure. However, established early warning scores designed to identify patients at risk of clinical deterioration were never validated in the obstetric population.

OBJECTIVE: This retrospective cohort study sought to evaluate the initial clinical characteristics of pregnant patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection and to develop a pregnancy-specific early warning score to identify patients at risk for clinical deterioration and requiring advanced respiratory support.

STUDY DESIGN: This was a single center, retrospective cohort study of pregnant patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection between April 2020 and December 2020. A total of 50 patients with severe acute respiratory syndrome coronavirus 2 infection between April 2020 and November 2020 were used to create the prediction model. Initial clinical characteristics identified at the time of diagnosis were compared between patients who required advanced respiratory support and those who were asymptomatic or had mild symptoms for those diagnosed during the period of April 2020 to November 2020. Risk factors associated with a requirement for advanced respiratory support were used to create the Obstetric Warning Score system. The Obstetric Warning Score system was then validated using 30 patients diagnosed with severe acute respiratory syndrome coronavirus 2 infection in December 2020. A receiver operating characteristic curve was generated to evaluate the test characteristics of the Obstetric Warning Score system compared with other scoring systems including the Early Warning Score, the National Early Warning Score, and the Maternal Early Warning Criteria.

RESULTS: Women who required advanced respiratory support were more likely to present with dyspnea (100% vs 33.3%; P<.001), have a higher heart rate (113.4 beats per minute vs 93 beats per minute; P<.001), respiratory rate (23.5 breaths per minute vs 17.7 breaths per minute; P<.001), temperature (99.1°F vs 98.3°F; P=.004), and C-reactive protein level (7.4 mg/dL vs 2.4 mg/dL; P<.001). Furthermore, 88.2% of patients requiring advanced respiratory support showed chest x-ray findings consistent with pneumonia, compared with 20.0% of the patients not requiring advanced respiratory support (P<.001). All patients requiring advanced respiratory support presented with at least 1 coronavirus disease 2019 symptom, whereas only 51.5% of patients not requiring advanced respiratory support were symptomatic (P<.001). The Obstetrical Warning Score model allocated 1 point each for a hazard ratio of >100 beats per minute, temperature of >99.0°F, C-reactive protein level of >2.0 mg/dL, respiratory rate between 20 and 24 breaths per minute, complaints of dyspnea, and a positive chest x-ray. A respiratory rate of >24 breaths per minute was assigned 2 points. The area under the curve for the Obstetric Warning Score system was 0.97 compared with 0.72 for the Early Warning Score system, 0.92 for the National Early Warning Score 2 system, and 0.85 for the Maternal Early Warning Criteria system. An Obstetric Warning Score ≥3 was predictive of a requirement for advanced respiratory support with a sensitivity of 100%, specificity 64%, and a positive predictive value of 36%.

CONCLUSION: The Obstetric Warning Score system presents a validated method for providers to identify pregnant patients who are at risk for respiratory failure and a requirement for advanced respiratory support.

Key words: COVID19, obstetric warning score, respiratory failure, prediction model

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China. Since the initial report, COVID-19 has spread to more than 210 countries and affected more than 80 million people globally, reaching pandemic status. In the United States, as of January 2021, there have been more than 20 million infections and 340,000 deaths. Existing literature suggests that patients infected with SARS-CoV-2 have variable clinical courses. It is suspected that 40% to 45% of infected patients are asymptomatic carriers. In pregnancy, asymptomatic carrier rates have been determined to be 74% to 78.6% compared with 46% in the general population. However, symptomatic patients may present with nonspecific respiratory, gastrointestinal, and musculoskeletal complaints and progress rapidly to severe respiratory failure. Case reports and case series suggest that the clinical course of COVID-19 may differ in pregnant patients compared with the general population. Specifically, the rate of

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severe disease requiring intensive care unit (ICU) admission is between 4.7% to 30%, and the mortality rate is as high as 15%. Pregnant patients with COVID-19 may be at higher risks for ICU admission, invasive ventilation, and extracorporeal membrane oxygenation compared with nonpregnant patients with COVID-19.

There are multiple early warning scoring systems used to identify symptomatic patients at risk for clinical deterioration. An early version of a COVID-19–specific early warning score (EWS) included chest computed tomography findings, contact history, fever, age, gender, respiratory symptoms, and neutrophil to lymphocyte ratio based on early cohort characteristics. Another commonly used scoring system was adapted from the National Early Warning Score (NEWS) initially developed in the United Kingdom to identify patients with critical illnesses. The NEWS includes respiratory rate, oxygen saturation, oxygen supplementation, systolic blood pressure, pulse, mental status, and temperature. Neither of these risk stratification systems account for the physiological changes that occur during pregnancy and therefore were never validated for use in pregnant patients.

The rapid spread of infection is exhausting hospital resources in certain areas of the country and limiting access to care for obstetrical patients. A risk stratification system that can rapidly identify SARS-CoV-2 infected pregnant patients at risk for clinical deterioration can help reduce the hospitalization burden and potentially provide early treatment to reduce COVID-19 severity. Therefore, we set out to design the Loma Linda Obstetric Warning Score (OWS) based on clinical data from pregnant patients with SARS-CoV-2 infection at our institution.

**Materials and Methods**

This was a single center, retrospective cohort study of gravid patients diagnosed with SARS-CoV-2 infection between April 2020 and December 2020. Starting from April 4, 2020, all obstetrical patients presenting to the labor and delivery (L&D) unit for delivery or triage were screened with 1 of the approved real-time polymerase chain reaction-based nasopharyngeal swab tests either on site or within 7 days of planned admission for delivery. Universal screening was performed regardless of the symptoms or history of sick contacts. All pregnant patients with a laboratory-confirmed SARS-CoV-2 infection who were evaluated in the L&D unit were included. Patients were excluded if they were transferred from another facility after intubation and more than 24 hours passed after an initial confirmatory test. This study was approved by the institutional review board (IRB # 5200166).

Obstetrical patients who screened positive for SARS-CoV-2, with or without symptoms of COVID-19, were recommended to undergo further clinical and laboratory risk assessments for clinical deterioration and need for respiratory support. In addition to routine clinical evaluation, laboratory evaluation included complete blood counts, complete metabolic panel evaluation, C-reactive protein (CRP), lactate, procalcitonin, pro-B-type natriuretic peptide (proBNP), and arterial blood gas concentrations, and a chest x-ray (CXR). The patients’ clinical outcomes were followed until delivery.

In addition to routine obstetrical indications for admission, patients with positive tests for SARS-CoV-2 were admitted if there was clinical evidence of pneumonia, including dyspnea, respiratory rate (RR) of >24 breaths per minute, pulse of ≥110 beats per minute (bpm), CXR consistent with pneumonia, fever of ≥100.4°F, or pulse oximetry <98% on room air. Patients admitted with the above clinical findings were given antenatal corticosteroid between 23 weeks 0 days and 36 weeks 5 days unless contraindicated. O2 supplementation was administered to patients with capillary O2 saturation at <95%.

Patients unable to maintain O2 saturation at ≥95% or normalize the respiratory rate to <24 breaths per minute with a nonrebreather mask delivering 10 liters/minute of O2 flow were started on high velocity nasal insufflation (Hi-VNI). Patients on Hi-VNI requiring more than 30 liters/minute and 65% fraction of inspired O2 (FiO2) in the obstetrical unit were transferred to the ICU, where endotracheal intubation and mechanical ventilation was performed if the patient decompensated further. Mild or asymptomatic patients were observed in the L&D unit for a maximum of 24 hours if they did not require O2 therapy.

Medical records were reviewed and abstracted for basic demographic information, presenting symptoms, initial vital signs, laboratory and CXR findings, and clinical course. The primary outcome of interest for this study was the need for advanced respiratory
support (ARS). This was defined as any patients who required Hi-VNI or mechanical ventilation.

A risk scoring system was generated based on patients diagnosed with SARS-CoV-2 infection between April 4, 2020, and November 30, 2020. For patients with a laboratory confirmed SARS-CoV-2 diagnosis during this time period, the initial clinical data, including basic demographic information, medical comorbidities, and initial laboratory and CXR findings, were compared between the patients who required ARS and patients who did not. The appropriate univariate statistical methods were used, depending on the type of variable, to identify risk factors associated with a need for ARS owing to COVID-19. Normally distributed continuous variables were compared using t tests; otherwise, the Wilcoxon rank-sum test was used. Dichotomous variables were evaluated using chi-square tests. A P value of <.05 was considered statistically significant. A P value adjustment for multiple comparisons was not made because we wanted to evaluate as many clinical variables as possible for inclusion in the prediction model.

Individual risk factors were assessed for their probably to predict a requirement for ARS by estimating the area under the curve (AUC) of receiver operating characteristic (ROC) curves. Risk factors for which the AUC was >0.5 were then reviewed for clinical relevance for inclusion in the prediction model. A forward stepwise elimination method was then applied to identify variables that maximized the ROC curve for predicting a requirement for ARS, starting with the 2 variables that had the highest individual AUCs. A new model was generated for each addition of a variable with the next highest AUC. The ROC curve for each new model was compared with the previous model to assess the change in the AUC. The final model was selected when addition of any other variable did not further increase the AUC compared with the previous model. The final model, named the Loma Linda OWS, was internally validated by applying the score to SARS-CoV-2–positive patients identified in December 2020. The ROC curve for the OWS score was compared against the EWS and NEWS2 using this internal validation cohort. In addition, we compared the OWS score with the Maternal Early Warning Criteria (MEWC). The MEWC is a pregnancy-specific EWS designed to identify obstetrical patients at risk for ICU admission. It was not evaluated specifically for COVID-19 infection.

All analyses were performed using the Stata software version 14 (StataCorp LLC, College Station, TX).

**Results**

Between April 4, 2020, and November 30, 2020, there were 51 obstetrical patients diagnosed with SARS-CoV-2 infection. One patient was excluded for being diagnosed postpartum. Therefore, 50 patients were included in the analysis for the prediction model development. In this cohort, 42 of 50 patients (84%) were Hispanic and 17 of 50 patients (34%) required ARS. Furthermore, 16 of 17 (94%) patients requiring ARS received remdesivir therapy, whereas patients who did not require ARS did not receive this treatment.

The median age of patients who required ARS was 31.5 years old (interquartile range [IQR], 27–35) compared with 28 years (IQR, 25–30) for the non-ARS group (P=.002). There were no differences in other maternal characteristics (Table 1). On initial presentation, all 17 patients who required ARS presented with dyspnea, compared with 11 of 33 (33.3%) of the non-ARS patients (P<.001). All ARS patients presented with at least 1 COVID-19 symptom, whereas only 17 of the 33 (51.5%) of non-ARS patients presented with COVID-19 symptoms.

### TABLE 1

**Demographics**

| Characteristics | Advanced respiratory support patients (n=17) | Asymptomatic or mild symptoms (n=33) | P value |
|-----------------|---------------------------------------------|--------------------------------------|--------|
| Maternal age (y)| 31.5 (27–35)                                | 28 (25–30)                           | .006   |
| BMI (kg/m²)     | 36.1±10.4                                   | 32.9±6.8                             | .20    |
| Gravidity       | 3 (2–5)                                     | 2 (1–3)                              | .11    |
| Parity          | 2 (1–3)                                     | 1 (0–2)                              | .11    |
| Gestational age (wk) | 30.7±4.6                              | 32.5±7.8                             | .38    |
| Race (Hispanic) | 13 (76.5)                                   | 29 (87.9)                            | .42    |
| Hypertension    | 3 (17.7)                                    | 4 (12.1)                             | .68    |
| Gestational hypertension | 2 (11.8)                              | 8 (24.2)                             | .46    |
| Diabetes        | 3 (17.7)                                    | 2 (6.1)                              | .40    |
| Asthma          | 3 (14.3)                                    | 2 (7.7)                              | .32    |

Data are presented as mean±SD, median (IQR), or n (%).

BMI, body mass index; IQR, interquartile range.

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### TABLE 2
Clinical signs and symptoms

| Signs and symptoms | Advanced respiratory support patients | Asymptomatic or mild symptoms | P value |
|--------------------|--------------------------------------|-----------------------------|---------|
| N                  | 17                                   | 33                          |         |
| Presenting symptoms|                                      |                             |         |
| Asymptomatic       | 0 (0)                                | 17 (51.5)                   | <.001   |
| Dyspnea            | 17 (100)                             | 11 (33.3)                   | <.001   |
| Cough              | 10 (58.8)                            | 7 (21.2)                    | .01     |
| Subjective fever   | 9 (52.9)                             | 7 (21.2)                    | .03     |
| GI symptoms        | 1 (5.9)                              | 3 (9.1)                     | 1.0     |
| Myalgia            | 4 (23.5)                             | 4 (12.1)                    | .42     |
| COVID-19 contact   | 7 (41.2)                             | 5 (15.2)                    | .08     |
| Decreased fetal movement | 0 (0) | 1 (3.0) | 1.0 |
| Rupture of membrane| 1 (5.9)                              | 3 (9.1)                     | 1.0     |
| Preterm labor      | 1 (5.9)                              | 0 (0)                       | .34     |
| Initial vital signs|                                      |                             |         |
| SBP (mm Hg)        | 117.2±16.7                           | 123±12.9                    | .13     |
| DBP (mm Hg)        | 65.8±12.0                            | 76.3±10.8                   | .003    |
| HR (beats per minute) | 113.4±20.0                      | 93±15.7                     | <.001   |
| RR (breaths per minute) | 23.5±6.8                      | 17.7±1.6                     | <.001   |
| Temperature (F)    | 99.1±1.3                             | 98.3±0.5                    | .004    |
| Pulse oximetly (%) | 96.6±3.2                             | 98.2±1.3                    | .03     |
| Initial laboratory findings | | | |
| WBC (bil/L)        | 8.7±3.4                              | 7.8±2.7                     | .33     |
| Neutrophil %       | 80.8±5.5                             | 72.9±11.6                   | .01     |
| Lymphocyte %       | 11.0±4.6                             | 18.2±10.3                   | .01     |
| NLR                | 13.1±21.1                            | 8.0±11.9                    | .35     |
| Platelet (bil/L)   | 234±80.1                             | 224±92.8                    | .70     |
| CRP (mg/dL)        | 7.4±3.6                              | 2.4±3.3                     | <.001   |
| Procalc (microg/L) | 0.93±2.9                             | 0.09±0.07                   | .26     |
| ProBNP             | 48.2±57.3                            | 159.5±225.7                 | .08     |
| Lactate (mmol/L)   | 1.1±0.4                              | 1.0±0.4                     | .52     |
| AST (U/L)          | 44.4±32.3                            | 27.9±23.1                   | .06     |
| ALT (U/L)          | 34.8±28.0                            | 24.0±18.6                   | .13     |
| PaO2 (mm Hg)       | 106.8±44.5                           | 90.3±24.9                   | .33     |
| PaCO2 (mm Hg)      | 28.3±5.0                             | 36.7±22.3                   | .20     |
| Chest x-ray        | 15 (88.2)                            | 6 (20.0)                    | <.001   |

Data are presented as mean±SD or n (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DBP, diastolic blood pressure; NLR, neutrophil/lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood cells.

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non-ARS patients were symptomatic ($P<.001$). Patients requiring ARS also had a higher heart rate ($113.4\pm20.0$ bpm vs $93\pm15.7$ bpm; $P<.001$), respiratory rate ($23.5\pm6.8$ breaths per minute vs $17.7\pm1.6$ breaths per minute; $P<.001$), and temperature ($99.1\pm1.3°F$ vs $98.3\pm0.5°F$; $P=.004$). Furthermore, 15 of 17 (88.2%) of the ARS patients showed CXR findings consistent with pneumonia compared with 6 of 33 (20.0%) of the non-ARS patients ($P<.001$). All other clinical characteristics were similar between the 2 groups (Table 2).

The optimal ROC curve model for patients requiring ARS included dyspnea, respiratory rate, heart rate, temperature, CRP, and CXR. The optimal cutoff that maximized sensitivity and specificity was a heart rate of $>100$ (bpm), a temperature of $>99.0°F$, and CRP of $>2.0$ mg/dL. One point was assigned to each of the clinical variables when values were above the optimal cutoff and for complaints of dyspnea and a CXR positive for pneumonia. In addition, an RR of between 20 and 24 breaths per minute was assigned 2 points (Box). The rate of positive findings for each of the clinical variables is tabulated in Table 3. The AUC of the OWS model was 0.97 (Figure 1).

The test performance of the OWS model was compared with the EWS, NEWS2, and MEWC models using a separate validation cohort based on patients diagnosed with SARS-CoV-2 infection between December 1, 2020, and December 31, 2020. During the month of December, 30 patients were diagnosed with SARS-CoV-2 infection and completed evaluation. In this group, 5 of 30 (16.7%) patients required ARS. The AUC for the OWS model applied to the validation cohort was 0.97 compared with 0.72 for the EWS, 0.92 for the NEWS2, and 0.85 for the MEWC (Figure 2). All 5 patients requiring ARS scored at least 3 points on the OWS model. Using an OWS score of $\geq3$ as the cutpoint for a positive screen for future ARS requirement showed a sensitivity of 100%, specificity of 64%, positive predictive value of 36%, and negative predictive value of 100%.

**Discussion**

**Principle findings**

Based on a pregnant SARS-CoV-2 cohort, we identified 6 important initial clinical characteristics to create a risk stratification model associated with a severe COVID-19 disease course requiring ARS. These include 1 point each for complaints of dyspnea, a heart rate of $>100$ bpm, temperature of $>99.0°F$, CRP of $>2$ mg/dL, and an abnormal CXR reading indicative of pneumonia. In addition, 1 point for a respiratory rate between 20 and 24 breaths per minute and 2 points for a respiratory rate of $>24$ breaths per minute were assigned.

The OWS score generated from these 6 clinical variables was a better predictor for a requirement of ARS for COVID-19 in the obstetrical population compared with the EWS, NEWS2, and MEWC. The AUC for the OWS was 0.97 compared with 0.72 for the EWS, 0.92 for the NEWS2, and 0.85 for the MEWC.

**Results**

The recent increase in prevalence of SARS-CoV-2 infection in pregnant patients presenting for care may overwhelm the medical system in certain geographic regions. In 1 report, more than 31.5% of obstetrical patients with SARS-CoV-2 infection were admitted

### TABLE 3

**Loma Linda Obstetrical Warning Score individual component**

| Initial clinical characteristics | Advanced respiratory support patients | Asymptomatic or mild symptoms | $P$ value |
|---------------------------------|--------------------------------------|-------------------------------|-----------|
| N                               | 17                                   | 33                            |           |
| Dyspnea                         | 17 (100)                             | 11 (33.3)                     | $<.001$  |
| Respiratory rate                |                                       |                               |           |
| $<20$                           | 8 (47.1)                             | 32 (97.0)                     | $<.001$  |
| $20-24$                         | 2 (11.8)                             | 1 (3.0)                       |           |
| $>24$                           | 7 (41.2)                             | 0 (0)                         |           |
| Heart rate $>100$               | 13 (76.5)                            | 10 (30.3)                     | .002     |
| Temperature $>99.0°F$           | 7 (41.2)                             | 3 (9.1)                       | .007     |
| C-reactive protein $>2$ mg/dL   | 17 (100)                             | 6 (30.0)                      | $<.001$  |
|                                 | 15 (71.4)                            | 2 (7.7)                       | $<.001$  |

Data are presented as n (%).

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compared with 5.8% of women of non-reproductive age. A pregnancy-specific warning system to identify patients at high risk for clinical deterioration is critical for triaging medical needs and resource allocation. Before this study, the EWS and NEWS2 scoring systems were not validated for use in obstetrical patients. For example, the EWS favored men older than 44 years, whereas the NEWS2 favored patients older than 65. Only the OWS score was specifically based on outcomes of an obstetrical cohort. An OWS score of greater than or equal to 3 has a sensitivity of 100% and a specificity of 64% in identifying patients who will require ARS.

Clinical implications

The US Food and Drug Administration (FDA) have approved several treatments for COVID-19 symptoms. These include remdesivir, baricitinib, casirivimab, and imdevimab to name a few. In addition, corticosteroids have been considered 1 of the main treatments for severe COVID-19 symptoms. There is limited evidence on the efficacy of these therapies in the pregnant population. However, despite a paucity of data, many of these treatments have been used during pregnancy for severe COVID-19. Furthermore, although the FDA approved the use of these medications for the treatment of severe COVID-19 infection specifically, earlier therapy may potentially prevent the onset of severe disease or reduce the disease burden. The ability to prevent severe COVID-19 disease presentation would be of particular interest in the pregnant population considering the risk for preterm delivery, a need for ARS, maternal death, and poor neonatal outcomes associated with a severe disease course. Because our study showed that the OWS score was efficient for triaging patients at risk for developing severe COVID-19 disease, it provides an opportunity for earlier treatment and possibly improved morbidity and mortality outcomes associated with COVID-19. Additional studies could help determine the clinical utility of the OWS score in combination with early therapy in reducing the disease burden of this infection.
Strengths and limitations
This obstetrical SARS-CoV-2 cohort were from a single academic institution. At our institution, very early in the course of the pandemic, we adopted a consistent management protocol for the initial assessment of COVID-19 in pregnancy. Therefore, one of the major strengths of our study is the consistency of management practices and near uniform collection of clinically relevant data. Furthermore, the prediction model was internally validated with a temporally separate obstetrical cohort. This study does suffer from some limitations. The data used to develop the prediction model and the validation data came from the same institution. Therefore, this scoring system and its clinical utility may be unique to the population at our institution. The sample size is small but consistent with other COVID-19 prediction models used in nonobstetrical cohorts. Additional studies are needed to validate this scoring system in other populations.

Conclusions
In pregnancy, severe COVID-19 cases were associated with a 21.2% preterm birth and 12.9% case fatality rate. The exponential increase in the rate of SARS-CoV-2 infection across the world further highlights the urgency to develop a patient triage system for appropriate healthcare resource allocation. It is our hope that the OWS prediction model can help to appropriately direct resources for pregnant patients and reduce the burden COVID-19 has placed on the healthcare system. Given the current global uncertainty in the long-term status of SARS-CoV-2 infections, it is likely that models such as the OWS will continue to have a clinical role in the management of pregnant COVID-19 patients in the foreseeable future.

Supplementary materials
Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajogmf.2021.100365.

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Author and article information
From the Department of Obstetrics and Gynecology, Loma Linda University School of Medicine, Loma Linda, CA (Drs Yao, Martin, Haase, Tse, Gheorghe, and Balli); Division of General Obstetrics and Gynecology, Loma Linda University School of Medicine, Loma Linda, CA (Drs Martin and Balli); Loma Linda University School of Medicine, Loma Linda, CA (Ms Nishino); Division of Maternal-Fetal Medicine; Loma Linda University School of Medicine, Loma Linda, CA (Drs Yao and Gheorghe).

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Corresponding author: Ruofan Yao, MD, MPH.
ryao@llu.edu