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Initial clinical characteristics of gravid SARS-CoV-2 positive patients and the risk of progression to severe COVID-19 disease

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AJOG at a Glance:

- This retrospective cohort study of gravid SARS-CoV-2 positive patients identified initial clinical characteristics associated with subsequent deterioration and need for advanced respiratory support.
- The obstetric warning score based on the initial clinical characteristics was validated using a separate cohort of patients.
- The obstetric warning score can help triage gravid patients with SARS-CoV-2 infection for inpatient observation versus outpatient management.

Abstract

OBJECTIVES: This retrospective cohort study sought to evaluate the initial clinical characteristics of pregnant patients diagnosed with SARS-CoV-2 infection, and to develop a pregnancy specific early warning score to identify patients at risk of clinical deterioration and requiring advanced respiratory support (ARS).

STUDY DESIGN: This was a single center retrospective cohort study of pregnant patients diagnosed with SARS-CoV-2 infection between April 2020 and December 2020. Fifty patients with SARS-CoV-2 infection between April and November were used to create the prediction model. Initial clinical characteristics identified at the time of diagnosis were compared between patients who required ARS and patients who were asymptomatic or had mild symptoms, using patients diagnosed between April and November 2020. Risk factors associated with ARS requirement were used to create the Obstetric Warning Score (OWS). The OWS score was then validated using 30 patients diagnosed with SARS-CoV-2 infection in December 2020. Receiver operator curve (ROC) was generated to evaluate the test characteristics of OWS compared to other scoring systems including the Early Warning Score (EWS), the National Early Warning Score 2 (NEWS2) and the Maternal Early Warning Criteria (MEWC).

RESULTS: Women who required ARS were more likely to present with dyspnea (100% vs. 33.3%, $p<0.001$), have higher heart rate (113.4 bpm vs. 93 bpm, $p<0.001$), respiratory rate (23.5 bpm vs. 17.7 bpm, $p<0.001$), temperature (99.1 ^{o}F vs. 98.3 ^{o}F, $p=0.004$) and C-Reactive Protein (CRP) (7.4 mg/dL vs. 2.4 mg/dL, $p<0.001$). Furthermore, 88.2% of ARS patients showed chest x-ray findings consistent with pneumonia, compared to 20.0% of non-ARS patients ($p<0.001$).

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All ARS patients presented with at least one COVID-19 symptom, while 51.5% of non-ARS patients were symptomatic (p<0.001). The OWS model included 1 point each for HR > 100 bpm, temperature > 99.0 ^{o}F, CRP >2.0 mg/dL, respiratory rate between 20 and 24 bpm, complaints of dyspnea and positive chest x-ray. Respiratory rate >24 bpm was assigned 2 points. The AUC for OWS is 0.97 compared with 0.72 for EWS, 0.92 for NEWS2 and 0.85 for MEWC. An OWS score ≥3 was predictive of ARS requirement with a sensitivity of 100%, specificity 64%, and positive predictive value of 36%.

CONCLUSIONS: The OWS presents a validated method for providers to identify pregnant patients who are at risk of respiratory failure and requiring advanced respiratory support (ARS).

Introduction

The Coronavirus disease 2019 (COVID-19) resulting from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China[1]. Since the initial report, COVID-19 has spread to more than 210 countries and affected 80 million people globally, reaching pandemic status[2]. In the United States, as of January 2021, there were more than 20 million infected and 340,000 deaths[3].

Existing literature suggests that patients infected with SARS-CoV-2 have a variable clinical course. It is suspected that 40-45% of infected patients are asymptomatic carriers[4]. In pregnancy, asymptomatic carrier rates have been cited at 74-78.6% compared with 46% in the general population[5–7]. However, symptomatic patients may present with non-specific respiratory, gastrointestinal and musculoskeletal complaints and progress rapidly to severe respiratory failure

[1,8,9]. Case reports and case series suggest the clinical course of COVID-19 may differ in pregnant patients compared to the general population. Specifically, the rate of severe disease requiring Intensive Care Unit (ICU) admission is between 4.7-30%, and the mortality rate as high as 15% [8,10–12]. Pregnant patients with COVID-19 may be at higher risks for ICU admission, invasive ventilation and extracorporeal membrane oxygenation compared to nonpregnant patients with COVID-19 [7,13].

There are multiple early warning scoring systems used to identify symptomatic patients at risk for clinical deterioration[14–16]. An early version of COVID-19 specific Early Warning Score (EWS) included chest CT findings, contact history, fever, age, gender, respiratory symptoms and neutrophil to lymphocyte ratio based on early cohort characteristics[1,17]. 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[18,19]. 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 physiologic changes that occur in 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 obstetric patients. A risk stratification system that can rapidly identify SARS-CoV-2 infected pregnant patients at risk for clinical deterioration can help reduce 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.

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Materials and Methods

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

Obstetric patients who screened positive for SARS-CoV-2, with or without symptoms of COVID-19, were recommended to undergo further clinical and laboratory risk assessment for clinical deterioration and need for respiratory support. In addition to routine clinical evaluation, laboratory evaluation included complete blood count (CBC), complete metabolic panel (CMP), c-reactive protein (CRP), lactate, procalcitonin, proB-type natriuretic peptide (proBNP), arterial blood gas (ABG) and chest x-ray (CXR). Patients' clinical outcomes were followed until delivery.

In addition to routine obstetrical indications for admission, patients with positive testing for SARS-CoV-2 were admitted if there was clinical evidence of pneumonia, including: dyspnea, respiratory rate (RR) >24 breaths per minute, pulse ≥110 beats per minute, chest x-ray consistent with pneumonia, fever ≥100.4 F, or pulse oximetry <98% on room air. Patients admitted with above clinical findings were given antenatal corticosteroid (ANCS) between 23 weeks 0 days

and 36 weeks 5 days unless contraindicated. Oxygen supplementation was administered to patients with capillary oxygen saturation <95%. Patients unable to maintain oxygen saturation ≥95% or normalize the respiratory rate to <24 breaths per minute with a non-rebreather mask delivering 10 liters/minute of oxygen 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 oxygen (FiO2) on the obstetric unit were transferred to the ICU, where endotracheal intubation and mechanical ventilation was performed if the patient further decompensated. Mild or asymptomatic patients were observed on L&D for a maximum of 24 hours if they did not require oxygen therapy.

Medical records were reviewed and abstracted for basic demographic information, presenting symptoms, initial vital signs, laboratory and chest x-ray 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 4th 2020 and November 30th 2020. For patients with laboratory confirmed SARS-CoV-2 diagnosis during this time period, 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 need for ARS due to COVID-19. Normally distributed continuous variables were compared using t-test, otherwise the Wilcoxon rank-sum test was used. Dichotomous variables were evaluated using chi square test. A p-value <0.05 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 predictability of ARS requirement by estimating the receiver operator curve (ROC). Risk factors where the area under the curve (AUC) was >0.5 were then reviewed for clinical relevance for inclusion in the prediction model. Forward stepwise elimination method was then applied to identify variables that maximized the ROC for predicting ARS requirement, starting with the two variables that had the highest individual AUCs. A new model is generated for each addition of a variable with the next highest AUC. ROC curve for each new model is compared with the previous model to assess the change in AUC. The final model was selected when addition of any other variable did not further increase the AUC compared to the previous model. The final model, named the Loma Linda Obstetric Warning Score (OWS), was internally validated by applying the score to SARS-CoV-2 positive patients identified in December of 2020. The ROC curve of the OWS score was compared against EWS and NEWS2 using this internal validation cohort. Additionally, we compared the OWS score to the Maternal Early Warning Criteria (MEWC). The MEWC was a pregnancy specific early warning score designed to identify obstetric patients at risk for ICU admission. It was not evaluate specifically for COVID-19 infection[20]. All analyses were performed using Stata 14 (College Station, TX).

Results

Between April 4th 2020 and November 30th 2020 there were 51 obstetric patients diagnosed with SARS-CoV-2 infection. One patient was excluded for being diagnosed postpartum. Therefore, 50 patients were included in the analysis for prediction model

development. In this cohort, 42/50 (84%) were Hispanic, and 17/50 (34%) required ARS. Furthermore, 16/17 (94%) ARS patients received remdesivir therapy. Whereas, patient who did not require ARS did not receive this treatment.

The median age of patients who required ARS was 31.5 years old (yo) inner quartile range(IQR) [27-35], compared with 28yo IQR [25-30] for the non-ARS group (p=0.002). There were no differences in other maternal characteristics (Table 1). On initial presentation, all 17 patients who required ARS presented with dyspnea, compared with 11/33 (33.3%) of non-ARS patients (p<0.001). All ARS patients presented with at least one COVID-19 symptom, whereas 17/33 (51.5%) of non-ARS patients were symptomatic (p<0.001). ARS patients also had higher heart rate (113.4±20.0 bpm vs. 93±15.7 bpm, p<0.001), respiratory rate (23.5±6.8 bpm vs. 17.7±1.6 bpm, p<0.001), and temperature (99.1±1.3 ^{o}F vs. 98.3±0.5 ^{o}F, p=0.004). Furthermore, 15/17 (88.2%) of ARS patients showed CXR findings consistent with pneumonia, compared with 6/33 (20.0%) of non-ARS patients (p<0.001). All other clinical characteristics were similar between the two groups (Table 2).

The optimal ROC model for ARS requirement included dyspnea, respiratory rate, heart rate, temperate, CRP and CXR. The optimal cut-point that maximized sensitivity and specificity was HR > 100 (bpm), temperature > 99.0 ^{o}F, CRP >2.0 mg/dL. One point each was signed above the optimal cutoff for each of the above clinical variables, as well as complaints of dyspnea and CXR positive for pneumonia. Additionally, RR ≥20 and <24 (bpm) was assigned 1 point. Whereas, RR ≥24 (bpm) was assigned 2 points (Box 1). 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 EWS, NEWS2 and MEWC models using a separate validation cohort, based on patients diagnosed with SARS-CoV-2 infection between December 1st and December 31st 2020. During the month of December, 30 patients were diagnosed with SARS-CoV-2 infection and completed evaluation. In this group, 5/30 (16.7%) required ARS. The AUC of the OWS model applied to the validation cohort was 0.97, compared with 0.72 for EWS, 0.92 for NEWS2 and 0.85 for MEWC (Figure 2). All five patients requiring ARS scored at least 3 points on the OWS model. Using OWS of ≥3 as the cutpoint for screen positive for future ARS requirement resulted in a sensitivity of 100%, specificity of 64%, positive predictive value (PPV) 36% and negative predictive value 100%.

Discussion

Principle findings

Based on a pregnancy specific SARS-CoV-2 cohort, we identified six important initial clinical characteristics to create a risk stratification model associated with severe COVID-19 disease requiring advanced respiratory support. These include one point each for complaints of dyspnea, heart rate >100 bpm, temperature >99.0 ^{o}F, CRP ≥2.0 mg/dL and abnormal CXR reading concerning for pneumonia. Additionally, one point for respiratory rate between 20 and 24 bpm, and two points for respiratory rate >24 bpm. The OWS score generated from these six clinical variables was a better predictor of ARS requirement for COVID-19 in the obstetric population compared to the EWS, NEWS2 and MEWC. The AUC for OWS was 0.97, compared with 0.72 for EWS, 0.92 for NEWS2 and 0.85 for 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 one report, more than 31.5% of obstetric patients with positive SARS-CoV-2 infection were admitted compared with 5.8% for women of non-reproductive age[21]. A pregnancy specific warning system to identify patients with high risk of clinical deterioration is critical for triaging medical needs and resource allocation. Prior to this study, the EWS and NEWS2 scoring systems were not validated for obstetric patients. For example, the EWS favored males older than 44[15]. Whereas, NEWS2 favored patients older than 65[16]. Only the OWS score was specifically based on outcomes of an obstetric cohort. An OWS score of greater than or equal 3 has a sensitivity of 100% and a specificity of 64% in identifying patients who will require ARS.

Clinical implications

The Food and Drug Administration (FDA) have approved several treatments for COVID-19 symptoms. These include remdesivir, baricitinib, casirivimab and imdevimab to name a few [22–24] . In addition, corticosteroids have been considered one of the main treatments for severe COVID-19 symptoms [25]. There is limited evidence on the efficacy of these therapies in the pregnant population. Yet, despite a paucity of data many of these treatments have been used during pregnancy for severe COVID-19 [26]. Furthermore, while 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 would be of particular interest in the pregnant population, considering the risk of preterm delivery, need for ARS, maternal death and poor neonatal outcomes

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associated with severe disease. Since our study showed that the OWS score was efficient in 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 obstetric SARS-CoV-2 cohort come 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. As a result, one of the major strengths of our study is the consistency of management practice and near uniform collection of clinically relevant data. Furthermore, the prediction model was internally validated with a temporally separate obstetric cohort. This study does suffer from some limitations. The data used to develop the prediction model and the validation data come from the same institution. Therefore, this scoring system and its clinical utility may be unique to the population to our institution. The sample size is low but consistent with other COVID-19 prediction models used in non-obstetric cohorts[1]. Additional studies are needed to validate this scoring system in other populations.

Conclusions

In pregnancy, severe COVID-19 cases were associated with 21.2% preterm birth and 12.9% case fatality rate [27,28]. The exponential increase in the rate of SARS-CoV-2 infection across the world further highlight the urgency in developing a patient triage system for appropriate healthcare resource allocation. It is our hope that the OWS prediction model can help

appropriately direct resources for pregnant patients and reduce the burden SARS-CoV-2 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 COVID-19 patients in pregnancy in the foreseeable future.

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Tables

Table 1: Demographics

	Advanced respiratory support patients	Asymptomatic or Mild Symptoms	p value
n	17	33	
Maternal age	31.5 [27-35]	28 [25-30]	0.006
BMI	36.1±10.4	32.9±6.8	0.20
Gravidity	3 [2-5]	2 [1-3]	0.11
Parity	2 [1-3]	1 [0-2]	0.11
Gestational age	30.7±4.6	32.5±7.8	0.38
Race (Hispanic)	13 (76.5)	29 (87.9)	0.42
Hypertension	3 (17.7)	4 (12.1)	0.68
Gestational hypertension	2 (11.8)	8 (24.2)	0.46
Diabetes	3 (17.7)	2 (6.1)	0.40
Asthma	3 (14.3)	2 (7.7)	0.32

*results presented as mean±SD, median[IQR], or n(%)

Table 2: Clinical Signs and Symptoms			
n	Advanced respiratory support patients 17	Asymptomatic or Mild Symptoms 33	p value
Presenting symptoms			
Asymptomatic	0 (0)	17 (51.5)	<0.001
Dyspnea	17 (100)	11 (33.3)	<0.001
Cough	10 (58.8)	7 (21.2)	0.01
Subjective fever	9 (52.9)	7 (21.2)	0.03
GI symptoms	1 (5.9)	3 (9.1)	1.0
Myalgia	4 (23.5)	4 (12.1)	0.42
COVID contact	7 (41.2)	5 (15.2)	0.08
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)	0.34
Initial vital signs			
SBP (mmHg)	117.2±16.7	123±12.9	0.13
DBP (mmHg)	65.8±12.0	76.3±10.8	0.003
HR (bpm)	113.4±20.0	93±15.7	<0.001
RR (bpm)	23.5±6.8	17.7±1.6	<0.001
Temperature (F)	99.1±1.3	98.3±0.5	0.004
Pulse oximetry (%)	96.6±3.2	98.2±1.3	0.03
Initial laboratory findings			
WBC (bil/L)	8.7±3.4	7.8±2.7	0.33
Neutrophil %	80.8±5.5	72.9±11.6	0.01
Lymphocyte %	11.0±4.6	18.2±10.3	0.01
NLR[1]	13.1±21.1	8.0± 11.9	0.35
Platelet (bil/L)	234±80.1	224± 92.8	0.70
CRP (mg/dL)	7.4±3.6	2.4±3.3	<0.001
Procal (microg/L)	0.93±2.9	0.09±0.07	0.26
ProBNP	48.2±57.3	159.5±225.7	0.08
Lactate (mmol/L)	1.1±0.4	1.0±0.4	0.52
AST (U/L)	44.4±32.3	27.9±23.1	0.06
ALT (U/L)	34.8±28.0	24.0±18.6	0.13
PaO2 (mmHg)	106.8±44.5	90.3±24.9	0.33
PaCO2 (mmHg)	28.3±5.0	36.7±22.3	0.20
Chest x-ray	15 (88.2)	6 (20.0)	<0.001
*results presented as mean±SD, or n(%)			
[1]NLR: Neutrophil/Lymphocite ratio			

Table 3: OWS individual component

	Advanced respiratory support patients	Asymptomatic or Mild Symptoms	p value
n	17	33	
Dyspnea	17 (100)	11 (33.3)	<0.001
Respiratory rate			
<20	8 (47.1)	32 (97.0)	<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)	0.002
Temperature >99.0F	7 (41.2)	3 (9.1)	0.007
C-reactive protein >2 mg/dL	17 (100)	6 (30.0)	<0.001
	15 (71.4)	2 (7.7)	<0.001

*results presented as n(%)

Box 1

Loma Linda Obstetric Warning Score	
Initial Clinical Finding:	**Points:**
Dyspnea	**1**
Heart rate > 100 bpm	**1**
Respiratory rate ≥20 and <24 bpm Respiratory rate ≥24 bpm	**1** **2**
Temperature >99.0 ^{o}F	**1**
C-reactive protein >2.0 mg/dL	**1**
Chest x-ray positive for pneumonia	**1**
Total points ≥3 high risk for clinical deterioration	

Figure Legends

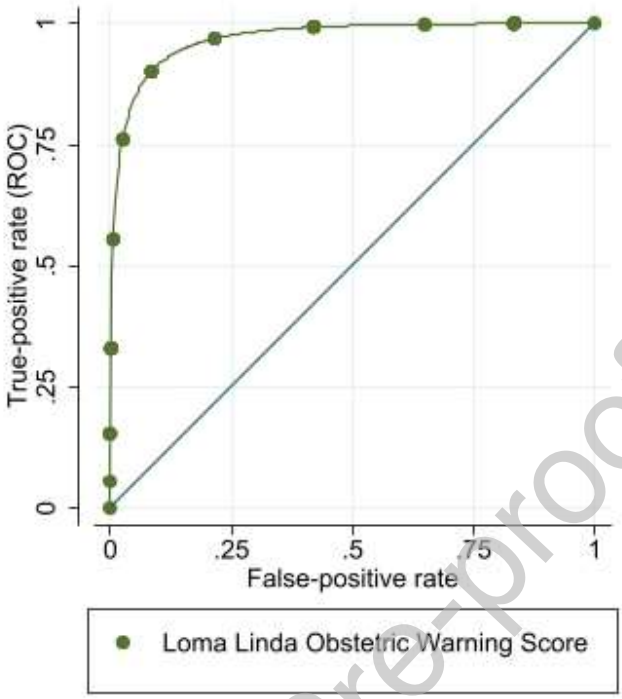

Figure 1: Receiver Operator Curve for prediction of advanced respiratory support using the Loma Linda Obstetric Warning Score (OWS) system. This model was based on laboratory confirmed SARS-CoV-2 positive pregnant patients diagnosed between April and November 2020. The Area under the curve of the OWS model was 0.97.

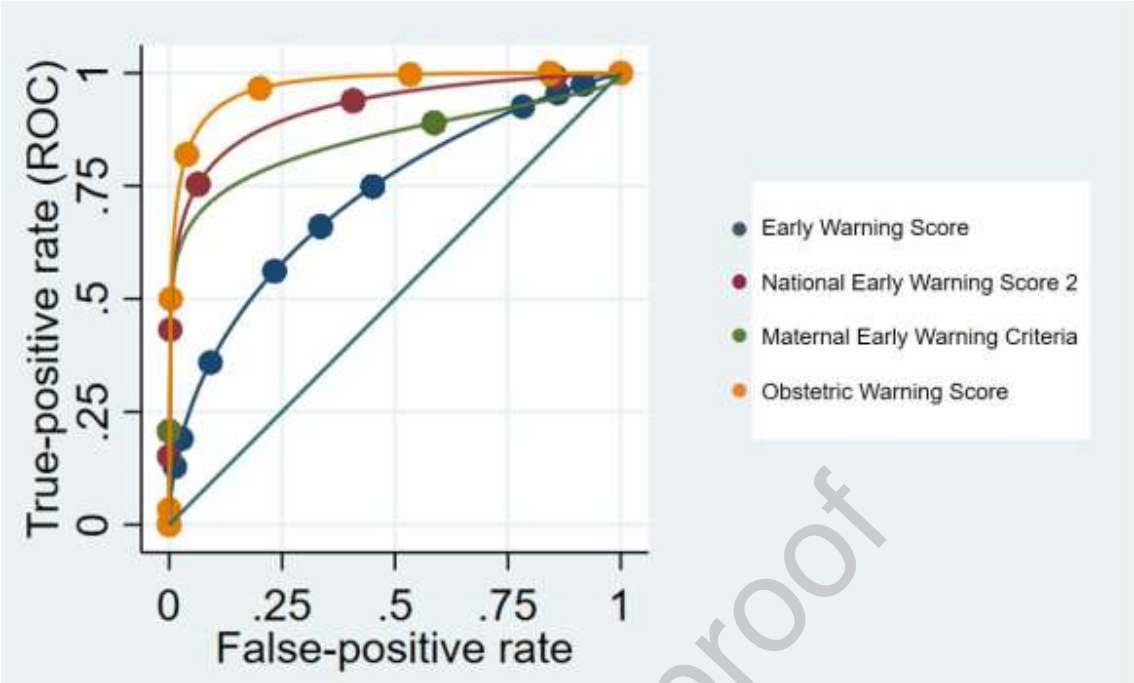

Figure 2: Validation of the OWS compared with EWS and NEWS2 for predicting pregnant SARS-CoV-2 patients at risk of requiring advanced respiratory support. EWS: Early Warning Score, Area under the curve (AUC) 0.72; NEWS2: National Early Warning Score 2, AUC: 0.92; MEWC: Maternal Early Warning Criteria, AUC: 0.85; OWS: Loma Linda Obstetric Warning Score, AUC: 0.96.