

Mechanical Ventilation and Death During Pregnancy Complicated by COVID-19: A Prognostic Analysis from the Brazilian COVID-19 Registry Score

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Abstract

Background

Assessing predictors of critical outcomes in COVID-19 may advise timely treatments and better prepare facilities to overcome extra adversities during pregnancy. However, many clinical parameters of existent scores are deeply modified by physiologic adaptations. Our aim was to assess the feasibility of a prognosis score developed for general hospitalized adults with COVID-19 in Brazil to predict clinical adverse outcomes in pregnant women upon hospital admission.

Methods

This is a multicenter retrospective substudy of the Brazilian COVID-19 Registry, a multicenter cohort analysis in Brazilian hospitals, which provided an accurate score to predict in-hospital death. The present analysis assessed the performance of this model, ABC₂-SPH, based on data of 3978 patients, to assess poor clinical outcomes in data from 85 pregnant women admitted due to COVID-19 from March 1, 2020, to May 5, 2021, in 19 Brazilian hospitals. The primary outcomes were death and the composite mechanical ventilation or death, and secondary were pregnancy outcomes and severe/critical Covid-19. The overall discrimination of the model was presented as the area under the receiver operating characteristic curve (AUROC).

Results

Thirty-one (36.5%) pregnant women had critical or severe COVID-19. Most of them had no previous comorbidities (64.7%). The median gestational age was 31.0 (26.0, 36.2) weeks; 38 (44.7%) women gave birth during hospitalization by Covid-19, most of them by C-section (76.3%). The need for mechanical ventilation or death occurred in 14 (17.3%) pregnant women. Severe and critical COVID-19 in pregnant women was associated with diabetes, inflammatory markers, and abnormal vital signals observed at admission. The model was not able to identify adverse clinical outcomes. The AUROC of predicting severe/critical Covid-19 illness was 0.595 (95% CI: 0.424-0.754); AUROC of the inpatient death discrimination was 0.683 (95% CI: 0.293-0.945), as the AUROC of mechanical ventilation or death discrimination was 0.591 (95% CI: 0.434-0.75).

Conclusions

The model ABC₂-SPH developed in Brazilian general patients was not able to identify adverse clinical outcomes in pregnant women with COVID-19. We warn against the use of general inpatients COVID-19 prognosis in pregnant women. A more useful model for clinical prognosis is necessary concerning the specificities of pregnancy affected by COVID-19.

Background

Coronavirus disease 19 (COVID-19) has quickly spread worldwide with higher morbidity and lethality than other coronaviruses (1), threatening people's lives, mainly those more vulnerable or under adverse social contexts (2, 3). Recent data raised concern about the impact of COVID-19 on pregnancy, since the pandemic severely hit more vulnerable countries with big birth rates (4-6). The impact of SARS-CoV-2 infection on pregnancy became more evident in controlled studies, revealing consistent increase in severe maternal morbidity and mortality and neonatal complications when comparing pregnant women with and without COVID-19 diagnosis (5). Pregnant women with comorbidities, such as diabetes, hypertensive diseases, heart disease and lung diseases deserve special attention, as they seem to be susceptible to the severe and critical forms of COVID-19, with higher risk of adverse outcomes (7).

Even though the majority of pregnant women are healthy and younger than most COVID-19 patients (8), during pregnancy there are significant anatomical and physiological changes that affect every organ system in the body (9). It is believed that such changes may interfere with the progression of COVID-19 (9, 10).

The assessment of clinical characteristics and outcomes in pregnant women who are hospitalized with COVID-19, as well as the factors potentially associated with adverse maternal outcomes in those patients, is of utmost importance for public health. It may help health managers and stakeholders to better prepare facilities to overcome extra-adversities during the pregnancy-puerperal period (8). However, rapid scoring systems for prognosis applicable during pregnancy are challenging. There are specificities in clinical parameters in pregnant women, so scores developed for non-pregnant cannot be applied in pregnant women without previous assessment. In this context, there is a lack of studies of risk or prognosis score for COVID-19 in pregnant women.

Therefore, the primary aim of this pilot study is to assess the ability of a COVID-19 prognosis score, developed for general hospitalized adults with COVID-19 in Brazil, to predict mechanical ventilation and death in pregnant women upon hospital admission. Additionally, to assess the occurrence of pregnancy adverse outcomes, as well as severe and critical COVID-19.

Methods

This is a multicenter retrospective substudy of the Brazilian COVID-19 Registry, a multicenter cohort study of consecutive patients with laboratory-confirmed COVID-19 hospitalized between March and September 2020, in 37 Brazilian public and private hospitals, as previously described (11, 12). It adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (13).

Study data were collected and managed by trained health professionals using Research Electronic Data Capture (REDCap) hosted at the Telehealth Center of the University Hospital, *Universidade Federal de Minas Gerais* (14, 15). Over three hundred variables were collected from medical records, involving clinical, laboratory and imaging characteristics at admission, as well as in-hospital outcomes related to COVID-19. Obstetric data were gestational age, pregnancy complications at admission, whether there was delivery and, if so, mode of delivery, birth weight and vital state of the newborn. The study protocol and a coding manual guiding data collection with details and the definition of each variable was agreed with the network of researchers (11).

This Registry study previously established a prognostic scoring model for in-hospital mortality for COVID-19 patients, based on comorbidities, clinical characteristics, laboratory and imaging findings at hospital presentation, the ABC₂-SPH score (12). The score has shown high discriminatory value (AUROC 0.844, 95% CI 0.829 to 0.859), which was confirmed in the Brazilian (0.859 [95% CI 0.833 to 0.885]) and Spanish (0.894 [95% CI 0.870 to 0.919]) validation cohorts, and displayed better discrimination ability than other existing scores (12).

For the score development and validation, patients who developed the first COVID-19 symptoms during admission due to other conditions and those who were admitted in another hospital first (not part of the cohort) were excluded, as the score was intended to be applicable upon hospital presentation. For the present analysis, the external validation group gathered data of pregnant women who were admitted from March 1, 2020, to May 5, 2021. We kept the first exclusion criteria, but opted to maintain women who were transferred between hospitals, as in Brazil only certain hospitals were selected to treat pregnant women with COVID-19 in the public health system, so if a pregnant women seek care in a non-reference center, she was transferred to a reference center and it would not be adequate to exclude those patients. After exclusion criteria, 85 pregnant women were identified in 19 of 37 multicentric network centers (Figure 1), in 12 different cities from 5 Brazilian states. Eight of them were public, 13 were teaching hospitals and 12 were reference centers for COVID-19 treatment, gathering average 322,8 beds (ranging from 60 to 784 beds).

Figure 1 Flowchart of COVID-19 pregnant women included in the study

Clinical characteristics, laboratory data and obstetric characteristics at admission, as well as events that occurred during hospital stay were collected for the present analysis.

Outcomes

The primary outcomes were death, and the composite outcome of mechanical ventilation or death. The secondary outcomes included pregnancy outcomes and the occurrence of severe and critical COVID-19, according to World Health Organization criteria (16). Pregnancy outcomes included preterm birth, c-section, preeclampsia, maternal death, and immediate neonatal vital state. Occurrence of severe and critical COVID-19 considered at least one of following conditions (16):

- Acute respiratory distress syndrome (ARDS), based on chest imaging and oxygenation impairment demanding mechanical ventilation.
- Sepsis, based on signs of organ dysfunction, including abnormal mental status, difficult or fast breathing, low oxygen saturation, renal failure, cardiac failure, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.
- Shock, based on persistent hypotension despite volume resuscitation, requiring vasopressors to maintain mean arterial pressure (MAP) \geq 65 mmHg and serum lactate level $>$ 2 mmol/L.
- Sequential Organ Failure Assessment (SOFA) score $>$ 2.
- Cardiac arrest, resuscitation or death.

- Severe pneumonia demanding ventilatory support, peripheral oxygen saturation (SpO₂) <90% on room air, respiratory frequency >30ipm had classification as severe COVID-19.

Statistical analysis

ABC₂-SPH development and validation methods followed guidance from the Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) checklist and Prediction Model Risk of Bias Assessment Tool (PROBAST), and are described elsewhere (12, 17, 18). In brief, generalized additive models (GAM) were used to examine the relationships between in-hospital mortality and potential predictors, selected based on clinical reasoning and literature review. Least absolute shrinkage and selection operator (LASSO) logistic regression was used to derive the mortality score, which was external validated (12).

Descriptive analysis of the pregnant women's clinical characteristics stratified by COVID-19 severity and the cohort of (non-pregnant) patients was performed, concerning the frequency, variability, and central tendency measures. Continuous variables were summarized using medians and interquartile ranges (IQR), whereas counts and percentages were used for categorical variables. For comparisons, the Chi-squared test or Fisher test was used for the independence hypothesis, and the Mann–Whitney test compared the numerical variables between the groups. A p-value less than 0.05 was considered statistically significant.

Calibration of the model applied to pregnant women was assessed graphically by plotting the predicted outcome of interest (death, composite outcome, or severe/critical disease) probabilities against the observed outcome, testing intercept equals zero and slope equals one. The area under the receiver operating characteristic curve (AUROC) described model's discrimination. Confidence intervals (95% CI) for AUROC were obtained through 2000 bootstrap samples.

Statistical analysis was performed with R software (version 4.0.2) with the tidyverse, pROC, rms packages.

Results

Clinical characteristics and laboratory findings of the 85 pregnant women upon hospital presentation are shown in Table 1. Their comparison to the ones who were excluded is shown in Table S3.

Table 1
Demographic and clinical characteristics at admission of the pregnant women included in the validation analysis

Label	Overall		Critical / Severe		Non Critical / Severe		P-value ²
Characteristic	N = 85 ¹	Non missing cases	N = 31 ¹	Non missing cases	N = 54 ¹	Non missing cases	
Age (years)	30.0 (26.0, 37.0)	85 (100%)	30.0 (27.0, 38.0)	31 (100%)	30.0 (26.0, 35.0)	54 (100%)	0.418
Comorbidities							
Hypertension	8 (9.4%)	85 (100%)	2 (6.5%)	31 (100%)	6 (11.1%)	54 (100%)	0.705
Diabetes mellitus	16 (18.8%)	85 (100%)	10 (32.3%)	31 (100%)	6 (11.1%)	54 (100%)	0.035
Obesity (BMI ≥ 30kg/m ²)	15 (17.6%)	85 (100%)	9 (29.0%)	31 (100%)	6 (11.1%)	54 (100%)	0.073
Symptoms*							
Adynamic	8 (9.4%)	85 (100%)	3 (9.7%)	31 (100%)	5 (9.3%)	54 (100%)	>0.999
Ageusia	12 (14.1%)	85 (100%)	2 (6.5%)	31 (100%)	10 (18.5%)	54 (100%)	0.196
Anosmia	17 (20.0%)	85 (100%)	2 (6.5%)	31 (100%)	15 (27.8%)	54 (100%)	0.037
Headache	25 (29.4%)	85 (100%)	9 (29.0%)	31 (100%)	16 (29.6%)	54 (100%)	>0.999
Rhinorrhea	19 (22.4%)	85 (100%)	5 (16.1%)	31 (100%)	14 (25.9%)	54 (100%)	0.439
Dyspnea	52 (61.2%)	85 (100%)	23 (74.2%)	31 (100%)	29 (53.7%)	54 (100%)	0.102
Sore throat	12 (14.1%)	85 (100%)	3 (9.7%)	31 (100%)	9 (16.7%)	54 (100%)	0.522

¹Statistics presented: Median (IQR); n (%)

²Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test; chi-square test of independence

BMI: body mass index; COPD: chronic obstructive pulmonary disease; HCO₃⁻: bicarbonate; NL ratio: neutrophils-to-lymphocytes ratio; pH: hydrogen potential;

pCO₂: carbon dioxide partial pressure; pO₂: oxygen partial pressure; SF ratio: SpO₂/FiO₂ ratio.

* There was no patient with neurological symptoms, arthralgia or skin rash

Label	Overall		Critical / Severe		Non Critical / Severe		P-value ²
Characteristic	N = 85 ¹	Non missing cases	N = 31 ¹	Non missing cases	N = 54 ¹	Non missing cases	
Fever	41 (48.2%)	85 (100%)	19 (61.3%)	31 (100%)	22 (40.7%)	54 (100%)	0.110
Myalgia	24 (28.2%)	85 (100%)	5 (16.1%)	31 (100%)	19 (35.2%)	54 (100%)	0.103
Nausea/vomiting	13 (15.3%)	85 (100%)	4 (12.9%)	31 (100%)	9 (16.7%)	54 (100%)	0.761
Productive cough	5 (5.9%)	85 (100%)	4 (12.9%)	31 (100%)	1 (1.9%)	54 (100%)	0.057
Clinical presentation upon hospital admission							
Glasgow coma score = 15	85 (100.0%)	85 (100%)	31 (100.0%)	31 (100%)	54 (100.0%)	54 (100%)	-
Respiratory rate (irpm)	22.0 (19.0, 25.0)	65 (76%)	25.0 (22.0, 26.5)	24 (77%)	20.0 (18.0, 23.0)	41 (76%)	0.003
SF ratio	457.1 (442.9, 466.7)	71 (84%)	440.5 (341.7, 461.9)	28 (90%)	461.9 (452.4, 466.7)	43 (80%)	0.003
Heart rate (bpm)	100.0 (92.0, 112.0)	81 (95%)	110.0 (98.0, 123.5)	31 (100%)	97.0 (90.2, 107.8)	50 (93%)	0.009
Systolic blood pressure		84 (99%)		31 (100%)		53 (98%)	0.016
≥ 90 (mm Hg)	80 (95.2%)		27 (87.1%)		53 (100.0%)		
Inotrope requirement	2 (2.4%)		2 (6.5%)				
Diastolic blood pressure		84 (99%)		31 (100%)		53 (98%)	0.166
≤ 60 (mm Hg)	15 (17.9%)		6 (19.4%)		9 (17.0%)		
¹ Statistics presented: Median (IQR); n (%)							
² Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test; chi-square test of independence							
BMI: body mass index; COPD: chronic obstructive pulmonary disease; HCO ₃ ⁻ : bicarbonate; NL ratio: neutrophils-to-lymphocytes ratio; pH: hydrogen potential;							
pCO ₂ : carbon dioxide partial pressure; pO ₂ : oxygen partial pressure; SF ratio: SpO ₂ /FiO ₂ ratio.							
* There was no patient with neurological symptoms, arthralgia or skin rash							

Label	Overall		Critical / Severe		Non Critical / Severe		P-value ²
Characteristic	N = 85 ¹	Non missing cases	N = 31 ¹	Non missing cases	N = 54 ¹	Non missing cases	
Inotrope requirement	2 (2.4%)		2 (6.5%)				
Laboratory exams							
Hemoglobin (g/L)	11.8 (10.8, 12.5)	82 (96%)	11.4 (10.6, 12.1)	31 (100%)	11.9 (11.0, 12.6)	51 (94%)	0.144
Platelet count (109/L)	201,000.0 (167,000.0, 243,000.0)	81 (95%)	183,500.0 (159,000.0, 213,250.0)	30 (97%)	217,000.0 (176,500.0, 252,500.0)	51 (94%)	0.064
NL ratio	4.9 (3.4, 7.1)	82 (96%)	6.7 (5.1, 8.5)	31 (100%)	3.7 (2.7, 5.9)	51 (94%)	<0.001
Lactate value	1.1 (0.8, 1.5)	34 (40%)	1.0 (0.7, 1.3)	18 (58%)	1.2 (0.9, 1.6)	16 (30%)	0.308
C reactive protein (mg/L)	47.0 (19.0, 100.0)	61 (72%)	90.4 (37.0, 162.6)	23 (74%)	33.1 (12.5, 64.1)	38 (70%)	0.001
Urea (mg/dL)	15.0 (11.2, 19.5)	62 (73%)	12.0 (9.9, 18.0)	25 (81%)	15.0 (13.0, 20.0)	37 (69%)	0.029
¹ Statistics presented: Median (IQR); n (%)							
² Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test; chi-square test of independence							
BMI: body mass index; COPD: chronic obstructive pulmonary disease; HCO ₃ ⁻ : bicarbonate; NL ratio: neutrophils-to-lymphocytes ratio; pH: hydrogen potential;							
pCO ₂ : carbon dioxide partial pressure; pO ₂ : oxygen partial pressure; SF ratio: SpO ₂ /FiO ₂ ratio.							
* There was no patient with neurological symptoms, arthralgia or skin rash							

Label	Overall		Critical / Severe		Non Critical / Severe		P-value ²
Characteristic	N = 85 ¹	Non missing cases	N = 31 ¹	Non missing cases	N = 54 ¹	Non missing cases	
Creatinine (mg/dL)	0.6 (0.5, 0.7)	72 (85%)	0.6 (0.5, 0.7)	28 (90%)	0.6 (0.5, 0.7)	44 (81%)	0.982
HCO ₃ ⁻	18.8 (17.2, 20.0)	42 (49%)	18.0 (17.0, 20.0)	22 (71%)	18.9 (18.0, 20.0)	20 (37%)	0.752
pH	7.4 (7.4, 7.5)	43 (51%)	7.4 (7.4, 7.5)	22 (71%)	7.4 (7.4, 7.5)	21 (39%)	0.105
Arterial pO ₂	85.3 (72.3, 105.6)	43 (51%)	84.7 (73.5, 103.0)	22 (71%)	87.6 (67.0, 104.2)	21 (39%)	0.903
Arterial pCO ₂	29.0 (26.2, 30.9)	43 (51%)	30.0 (25.2, 33.4)	22 (71%)	29.0 (27.0, 30.0)	21 (39%)	0.395
¹ Statistics presented: Median (IQR); n (%)							
² Statistical tests performed: Wilcoxon rank-sum test; Fisher's exact test; chi-square test of independence							
BMI: body mass index; COPD: chronic obstructive pulmonary disease; HCO ₃ ⁻ : bicarbonate; NL ratio: neutrophils-to-lymphocytes ratio; pH: hydrogen potential;							
pCO ₂ : carbon dioxide partial pressure; pO ₂ : oxygen partial pressure; SF ratio: SpO ₂ /FiO ₂ ratio.							
* There was no patient with neurological symptoms, arthralgia or skin rash							

Table 1 Characteristics of the pregnant women included in the validation analysis, according to COVID-19 severity

The majority of the included pregnant women had no previous comorbidities (64.7%). Diabetes mellitus (18.8%), obesity (17.6%), and chronic hypertension (9.4%) were the most frequent diseases. Thirty one (36.5%) developed critical or severe COVID-19. Hypertensive disorders compromised 16 (18.8%) patients, with no difference between groups of COVID-19 severity (p=0.702). Diabetes was more frequent in the severe/critical COVID-19 women (32.3% vs. 11.1%, p=0.035).

Dyspnea (61.2%), headache (29.4%) and myalgia (28.2%) were the most frequent symptoms, and the frequency of symptoms was similar between the groups of severity, except for anosmia, more frequent in the non-severe/critical group (27.8%) when compared with the severe/critical one (6.5%). With regards to clinical presentation upon hospital admission, patients who developed severe/critical disease also had significantly lower median SpO₂/FiO₂ ratio, higher median respiratory and heart rates, higher median neutrophils-to-lymphocytes ratio and C-reactive protein, and slightly lower median urea values than the ones who did not developed severe disease (Table 1).

Concerning obstetric characteristics (Table 2), the median gestational age was 31.0 (26.0, 36.2) weeks overall, and there was no difference with regards to COVID-19 severity (31.0 [27.5-34.0] vs. 32.0 [26.0-38.0],

p=0.472). Thirty-eight (44.7%) women gave birth, most of them by C-section (76.3%), with a non-significant difference between groups (87.5% in severe/critical group vs. 68.2% in non-severe one, p=0.254). One woman delivered twins, totaling 39 newborns, 38 (97.4%) of them alive at hospital discharge. Birth weight, five-minute Apgar score, and being born alive were similar between groups.

Table 2
Characteristics of the newborns of women with birth during COVID-19 hospital stay

Label	Overall		Critical / Severe		Non Critical / Severe		P-value ²
Characteristic	N =85 women / 39 newborns ¹	Non missing cases	N = 31 ¹	Non missing cases	N = 55 ¹	Non missing cases	
Gestational age (weeks)	31.0 (26.0, 36.2)	84 (99%)	31.0 (27.5, 34.0)	31 (100%)	32.0 (26.0, 38.0)	53 (98%)	0.472
Gestational hypertensive disorder	16 (18.8%)	85 (100%)	7 (22.6%)	31 (100%)	9 (16.7%)	54 (100%)	0.702
Gestational complication	32 (39.0%)	82 (96%)	16 (51.6%)	31 (100%)	16 (31.4%)	51 (94%)	0.112
Vaginal birth or C-Section		38 (45%)		16 (52%)		22 (41%)	0.254
Cesarean	29 (76.3%)		14 (87.5%)		15 (68.2%)		
Natural birth	9 (23.7%)		2 (12.5%)		7 (31.8%)		
Childbirth	37 (45.1%)	82 (96%)	16 (51.6%)	31 (100%)	21 (41.2%)	51 (94%)	0.489
Born alive	38 (97.4%)	39 (45%)	16 (100.0%)	16 (52%)	22 (95.7%)	23 (42%)	>0.999
Birth weight	3,040.0 (2,430.0, 3,365.0)	33 (38%)	2,622.5 (2,086.2, 3,392.0)	14 (45%)	3,050.0 (2,725.0, 3,290.0)	19 (35%)	0.689
Apgar Score	8.0 (7.0, 9.0)	34 (40%)	8.0 (6.2, 8.8)	14 (45%)	8.0 (7.8, 9.0)	20 (36%)	0.410
¹ Statistics presented: n (%); Median (IQR)							
² Statistical tests performed: Fisher's exact test; Wilcoxon rank-sum test							

Table 2 Characteristics of pregnancy at admission and newborns of women with birth during COVID-19 hospital stay

The comparison between the pregnant women included in the pilot validation and the ABC₂-SPH model-derivation cohort is shown in Table S1, and Table S2. Pregnant women were markedly younger than the

group of patients who derived the model of prediction (30 [26–37] vs. 60 [48-72] years-old, $p<0.001$), and they had a lower frequency of comorbidities. Coronary artery disease, heart failure, atrial fibrillation/flutter, stroke, and chronic obstructive pulmonary disease (COPD) were not observed among the pregnant group. There were significant differences comparing laboratory findings and vital signals between groups, such as lower hemoglobin levels (11.8 [10.8-12.5] vs. 13.3 [12.1-14.5], $p<0.001$), higher heart rate (median 100 [92-112] vs. 88[78-100] bpm, $p<0.001$), and higher SpO_2/FiO_2 ratio (457.1 [442.9-366.7] vs. 428 [332.1-452.4], $p<0.001$) in pregnant women.

With regards to patient outcomes (Table 2), in-hospital mortality was 20.4% and 3.5% for the model-derivation cohort compared to the pregnant women ($p<0.001$). Hospital and intensive care unit length of stay were also longer in the general group of patients than pregnant women ($p=0.010$ and $p=0.048$, respectively).

Fourteen pregnant women needed mechanical ventilation (17.3%), and 3 (3.5%) died in hospital. All of the dead women needed mechanical ventilation. The ABC₂-SPH model was not able to identify high-risk pregnant women (Figure 2). Discrimination was poor for inhospital mortality (area under the ROC curve [AUROC] 0.683 [95% CI: 0.293-0.945]), the composite mechanical ventilation or death (AUROC 0.591 [95% CI: 0.434-0.75]), and for predicting severe or critical COVID-19 (AUROC 0.595 [95% CI: 0.424-0.754]) (Figure 3).

Figure 2 Discrimination of ABC₂-SPH Score in the sample of pregnant women (n=85) to predict death (A), death or mechanical ventilation (B) or critical disease (C)

Figure 3 The observed and expected death (A), composite of mechanical ventilation or death (B) and severe/critical COVID-19 (C), for each quartile of pregnant women risk

Discussion

The main contribution of present analysis was testing the ABC₂-SPH model developed from a cohort of 3978 patients (12), based on clinical and laboratory characteristics upon hospital presentation, in an external validation with 85 pregnant women from 19 Brazilian hospitals. Even though the ABC₂-SPH model presented very high discrimination in external validation in cohorts of general hospitals (12), this model failed to discriminate the adverse clinical results in pregnant women. Calibration curves showed that the ABC₂-SPH model overestimated the risk of death, or the composite of mechanical ventilation or death in pregnant women. Additionally, the risk of severe/critical progression of COVID-19 was underestimated in cases of low probability and overestimated in cases of higher probability of the outcome (Figure 2).

Our interpretation is that the set of prognosis markers of COVID-19 in pregnancy are not the same as the ones for the non-pregnant population admitted with the disease. This finding itself could contribute to an understanding of the poor outcomes as COVID-19 maternal mortality. According to Brazilian data, pregnancy complicated by COVID-19 is a serious burden for the hospital maternity services. Pregnant women accounted for 0.8/1000 of 20,350,142 confirmed cases in the country until Aug/2021 (19, 20). However, the rate of mortality was 10.5%, 3.8 times higher than the rate of 2.8% of the national mortality (19).

Across the studies in non-pregnant populations, male sex, increasing age and underlying illness, such as cardiovascular diseases and diabetes, increased the risk of poor outcomes (21, 22). The ABC₂-SPH predictive model was developed upon a set of covariates upon hospital presentation to predict death: age, chronic diseases (hypertension, diabetes mellitus, obesity, coronary artery disease, heart failure, atrial fibrillation or flutter, cirrhosis, cancer, chronic obstructive pulmonary disease and previous stroke), heart rate and SpO₂/FiO₂ ratio, allied to low platelets, C-reactive protein and urea (12). Such predictors might score differently in pregnant women, since they are deeply modified by physiologic adaptations, such as the increase in heart rate, which itself may overestimate the risk estimated by the score in at least 5%, and maternal response to infections. Our analysis reveals how distinct these groups are in terms of age, laboratory analysis, and in-hospital complications. Previous diabetes, blood pressure, respiratory rate, heart rate, SpO₂/FiO₂ ratio, neutrophils-to-lymphocytes ratio, and blood urea nitrogen at admission as associated with severe COVID-19. Preexisting comorbidities as diabetes and chronic hypertension have been shown to be associated with an increased risk for COVID-19 adverse outcomes in pregnant women (23, 24).

Most pregnant women were young and healthy before the admission due to COVID-19, which partially explains why abnormal vital signals and inflammatory markers are associated with the in-hospital severe/critical progression, instead of pre-existent comorbidities. Neutrophil-to-lymphocyte ratio and C-reactive protein were higher in the severe and critical COVID-19 group when compared to mild one. In fact, this ratio has been observed to be the most consistent abnormal hemocytometric finding in COVID-19 patients (25). In the multivariate modeling of ABC₂-SPH score (12), C-reactive protein is the inflammatory marker which was significant in the final model. We hypothesize that inflammatory markers could be covariables even more relevant for pregnant women, scoring proportionally higher than for general patients. Besides, physiological adaptations to the pregnancy affect the organ system in the maternal body, modifying, as well the response to infections.

The existing evidence is conflicting on whether pregnancy is an immunological contributor to severe progression of COVID-19 (26). A successful pregnancy depends on a responsive immune system, which explains reports of universal COVID-19 testing during pregnancy, that the vast majority is asymptomatic or has mild COVID-19 (26, 27). The unit maternal and feto-placental immune system is responsive, protecting both the mother and the fetus against treats from the environment (28). The placenta is a selective barrier, able to protect the developing fetus against infections, including SARS-CoV-2 virus infection (29). It also acts as an immunity-modulating organ, regulating immune responses of cells present both at the implantation site and systemically (30). However, evidence of fetal vascular malperfusion or thrombosis has been observed in COVID-19, which may be related to an exacerbated maternal systemic inflammatory response and hypercoagulable state (31, 32).

Notwithstanding, cardiopulmonary adaptive changes during pregnancy may increase the risk of hypoxemia and contribute to the increased severity of viral infections (33). The circulatory system is significantly adjusted during pregnancy, starting early in its course, driven by peripheral vasodilatation, increased heart rate and stroke volume, reduced pulmonary vascular resistance, and reduced pulmonary residual capacity. These changes may affect the course of viral infections (9, 33). For these reasons, although we believe that vital signals at admission might contribute to scoring in predictive models of COVID-19 outcomes during

pregnancy, the expected cut offs are affected by physiological changes during pregnancy and might not coincide with non-pregnant women. Besides, with hemodilution and rising glomerular filtration rate, there are modifications in the reference values for hemoglobin levels, proteins, creatinine, and urea (9), interfering in the performance of scores based on laboratory values. Therefore, it is comprehensible that scores used to predict mortality in general adults have limitations when used among pregnant women (34).

Another aspect of COVID-19 disease in pregnant women grounds on the overactivated renin–angiotensin system. This system plays a relevant role in maternal hemodynamic adaptations and in placentation and hypertensive disturbs during pregnancy (35). SARS-CoV-2 uses the protein angiotensin-converting enzyme the receptors 2 (ACE2) to invade cells, with potential implications for increased susceptibility to the virus during pregnancy (36). Obstetric outcomes were not the target in the current approach, even though they could be affected by COVID-19 (3, 5, 37).

Yet, this analysis has expected limitations that may affect the interpretation. Our sample size of pregnant women is limited. Maternal mortality was lower than Brazilian national rates (20), and the frequency of chronic hypertension was low. A specific predictive model for COVID-19 prognosis for inpatient pregnant women was not proposed. The results also do not apply to antenatal care since the inclusion criteria was pregnant women admitted with COVID-19. As a retrospective analysis, the quality of data as incompleteness might have occurred. Thus, we reduced the risk of inaccuracies by performing several quality checks and rechecking hospital medical records whenever necessary.

Based on our results, we warn against the use of non-pregnant COVID-19 prognosis scores in pregnant women to predict adverse outcomes without proper validation. While insufficient control of pandemic keeps worldwide, fast and efficient assessment of prognosis of the COVID-19 is of utmost importance for early identification of cases at higher risk of worse outcome in this highly vulnerable group of women. Although several studies developed and validated risk scores to estimate prognosis in COVID-19 patients, there is a lack of scores focused on pregnant women specificities. Studies using data pools across national systems or healthcare data sharing frameworks are necessary to rapidly join and use clinical information relevant to COVID-19 during the pregnancy. Martinez-Portilla et al. reported a national model to predict death among women of reproductive age with COVID-19, highlighting pregnancy as a risk factor for death, pneumonia and intensive care unit admission (38); however without proposing a prediction model. Villar et al. provided consistent evidence that COVID-19 substantially increases maternal morbidity and mortality, and neonatal complications, in a multinational prospective cohort study, without proposing a risk score (5). Evidence-based modelling could provide a proper prognosis score assessment tool that will help guide decision-making, develop patient care plans, and better allocate resources. Additionally, we believe that a team of intensive care with the support of obstetrics specialists is necessary to make better decisions around COVID-19 upon pregnancy, identifying and prioritizing the care of those who have a higher risk of morbidity and mortality.

Conclusions

In conclusion, this study has shown that the model ABC₂-SPH developed in Brazilian general patients was not able to identify adverse clinical outcomes in pregnant women with COVID-19. Prognosis markers of the COVID-19 clinical evolution upon pregnancy are not the same as the in-hospital population admitted with the disease. We warn against the use of general inpatients COVID-19 prognosis in pregnant women. A more useful model for clinical prognosis is necessary concerning the specificities of pregnancy affected by COVID-19.

Abbreviations

ACE2

Angiotensin-Converting Enzyme the Receptors 2

ARDS

Acute respiratory distress syndrome

AUROC

Receiver Operating Characteristic Curve

BMI

body mass index

COPD

Chronic Obstructive Pulmonary Disease

COVID-19

Coronavirus Disease 2019

FiO₂

Fraction Of Inspired Oxygen

GAM

Generalized Additive Models

HCO₃⁻

bicarbonate

IQR

Interquartile Ranges

LASSO

Least Absolute Shrinkage and Selection Operator

MAP

Mean Arterial Pressure

NL ratio

neutrophils-to-lymphocytes ratio

pCO₂

carbon dioxide partial pressure

pH

hydrogen potential

pO₂

oxygen partial pressure

PROBAST

Prediction Model Risk of Bias Assessment Tool

REDCap

Research Electronic Data Capture

SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus 2

SF ratio

SpO₂/FiO₂ ratio

SOFA

Sequential Organ Failure Assessment

SpO₂

Peripheral Oxygen Saturation

STROBE

Strengthening the Reporting of Observational Studies in Epidemiology

TRIPOD

Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Brazilian National Commission for Research Ethics (CAAE 30350820.5.1001.0008). Individual informed consent was waived due to the severity of the situation and the use of unidentified data, based on medical chart review only. Additionally, administrative permissions to access and use the medical records were obtained from each institution.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MSM, MCP, ZSNR had substantial contributions to the conception or design of the work. ZSNR, RALPA, TLSS, AOM, ALBAS, BLF, CMR, CCRC, CSC, CR, DP, EC, EMSK, ERFM, FFMGA, FA, GPC, GANB, JCA, JMR, KBR, LBZ, LSP, LYBC, LEAS, MAF, MFLM, MHGJ, PJLM, RSCA, RCM, RP, RLSM, MCP, MSM had substantial contributions to the acquisition, analysis, or interpretation of data for the work. All authors read and approved the final manuscript.

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Figures

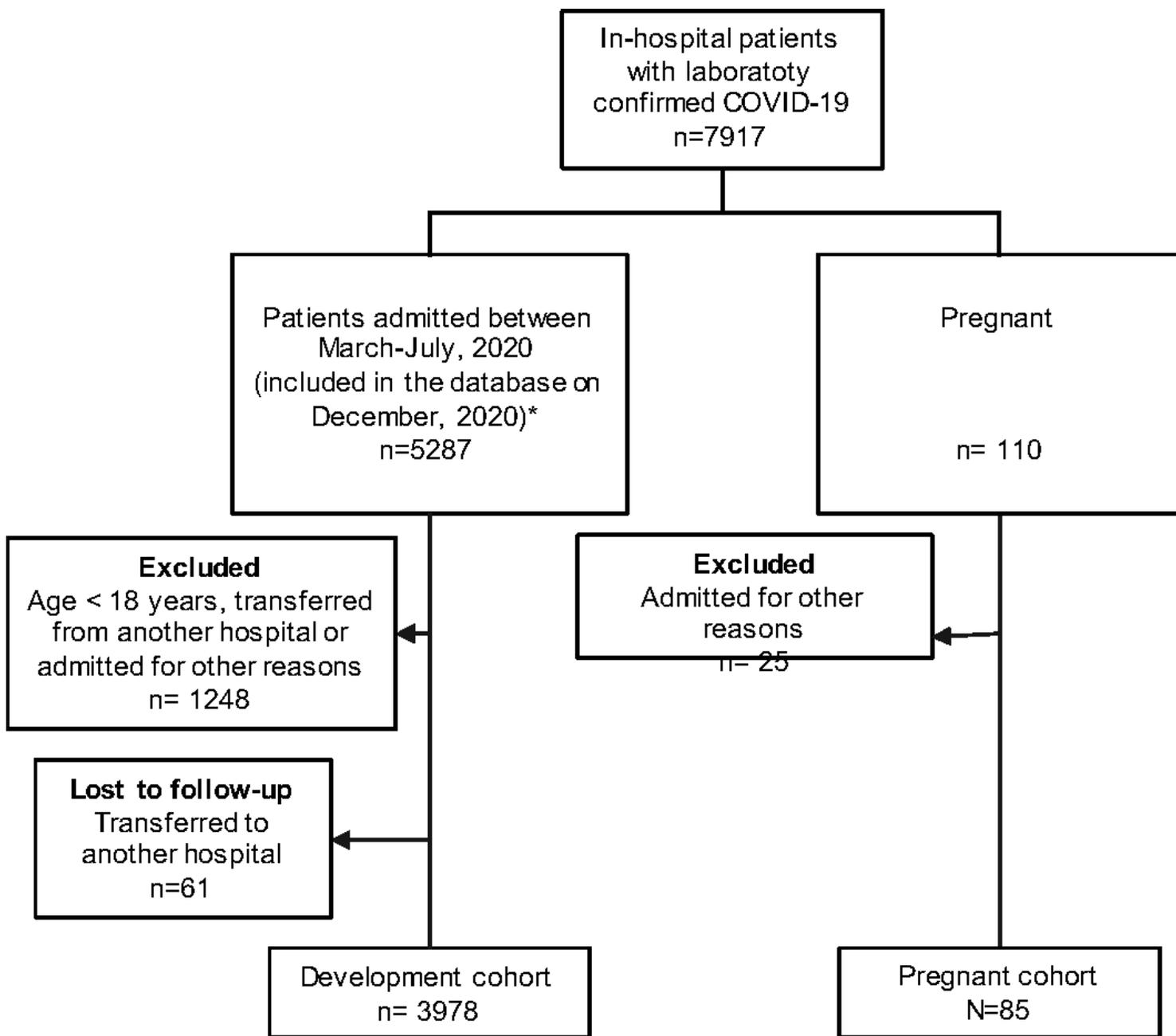


Figure 1

Flowchart of COVID-19 pregnant women included in the study

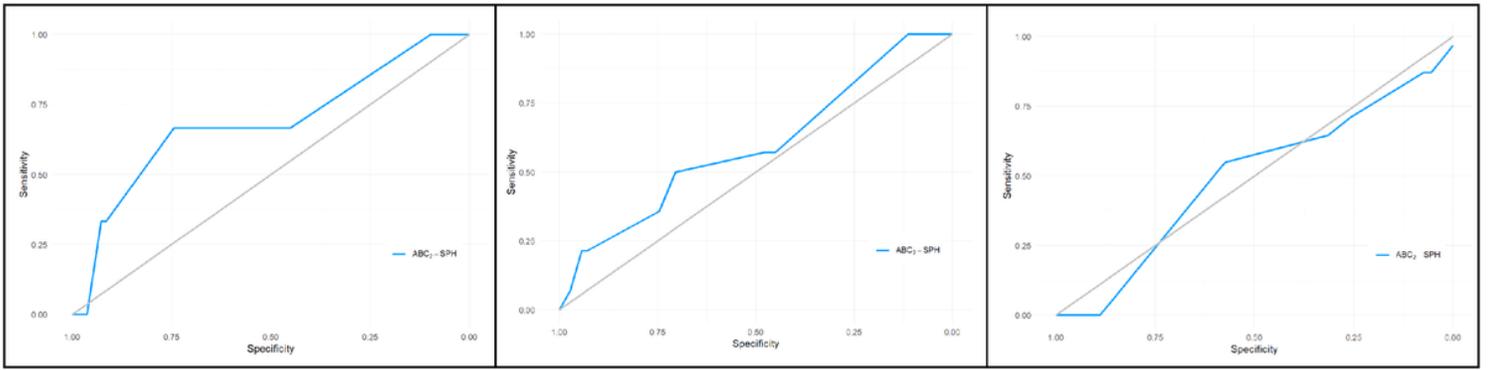


Figure 2

Discrimination of ABC₂-SPH Score in the sample of pregnant women (n=85) to predict death (A), death or mechanical ventilation (B) or critical disease (C)

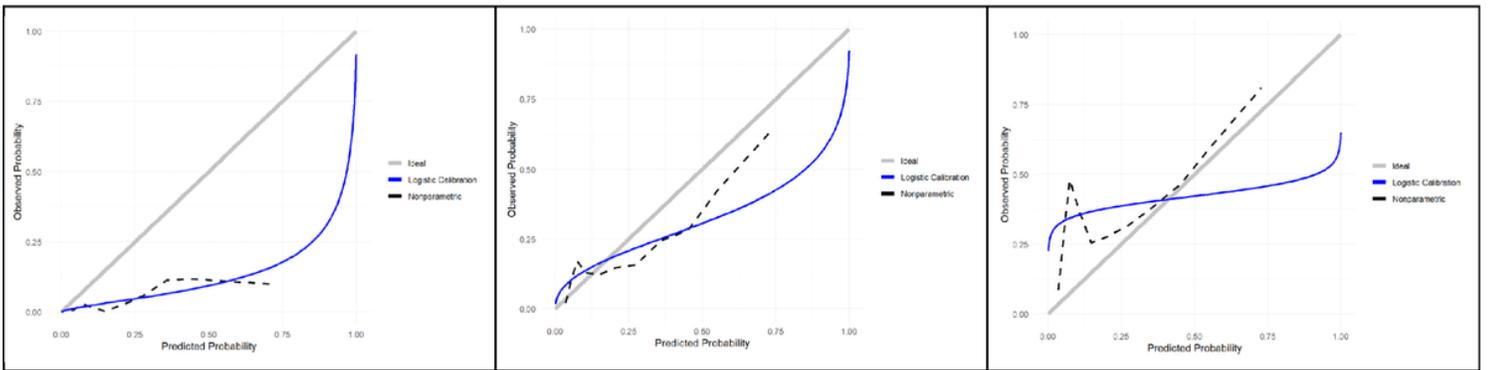


Figure 3

The observed and expected death (A), composite of mechanical ventilation or death (B) and severe/critical COVID-19 (C), for each quartile of pregnant women risk

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