SFIT-1 for the prediction of adverse maternal outcomes in women with SARS-CoV-2 infection and hypertensive disorders of pregnancy

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Objective
The aim of this study is to evaluate the association of sFlt-1 as a predictor of adverse maternal outcome among women with hypertensive disorders of pregnancy and confirmed SARS-CoV-2 infection.

Methods
This is a multicenter retrospective cohort study of women with confirmed SARS-CoV-2 infection that required hospital admission at the Instituto Nacional de Perinatología, Hospital de la Mujer, and the Hospital General de Mexico. The exposed cohort comprised women with a diagnosis of a hypertensive disorder of pregnancy that included preeclampsia, eclampsia, and HELLP syndrome according to ACOG criteria between October 2020 and December 2021. Controls were those hospitalized pregnant women with confirmed SARS-CoV-2 infection and no hypertension in pregnant. Biomarkers (sFlt-1 and PI GF) were log-transformed and converted to their multiples of the median (MoM) according to the Fetal Medicine Foundation algorithms. The primary outcome was the composite definition of adverse maternal outcome that comprised any of the following: maternal pneumonia, acute kidney disease, multiple organ failure, maternal sepsis, maternal death, preterm rupture of membranes, and threatened preterm labour. Secondary outcome was the composite of adverse fetal and neonatal outcomes that comprised the following: prematurity, small-for-gestational age neonate, fetal growth restriction, caesarean section due to fetal distress, low Apgar score, Grade IV intraventricular hemorrhage, respiratory distress syndrome, neonatal sepsis, neonatal death, admission to the neonatal intensive care unit. The association between predictors and the main and secondary outcomes was assessed using an elastic-net regression which comprised a Lasso and Ridge regression method for automatic variable selection and penalization of non-statistically significant coefficients using a 10-fold cross-validation where the best model if automatically chosen by the lowest Akaike information criterion (AIC) and Bayesian information criteria (BIC). Predictive probabilities of an adverse outcome were calculated for the multivariate model adjusted by possible confounders selected by the elastic-net regression using the interaction between sFlt-1 and hypertensive disorders of pregnancy (HDP) in a full factorial model for graph purposes. p-values <0.05 were considered statistically significant.

Results
One hundred forty-eight women with a positive RT-qPCR test for SARS-CoV-2 infection admitted to the hospital were included, of which 56 (37.8%) had an HDP. The mean maternal age was 30 (range: 15-45) years. There were significant differences on mean arterial pressure (MAP) [84.16 (80-90.5) vs. 117 (96.3-124.3); p<0.001], platelet count [213 (185-269) vs. 183 (145-230); p<0.001], ALT [19 (12-35.5) vs. 47 (26-78); p<0.001], AST [23 (17-35) vs. 36 (19-85); p<0.001], troponin [1.2 (0.3-2.1) vs. 2.3 (1.1-6.7); p=0.034], myoglobin [18.9 (13.2-31.1) vs. 32.6 (18-54); p=0.027], sFlt-1 MoMs [0.789 (0.545-1.758) vs. 2.47 (1.0-5.22); p<0.001], and sFlt/PI GF ratio [15.96 (6.42-53.09) vs. 189 (63.89-489.02); p<0.001]. Women with HDP had higher incidence of pneumonia (66.1% vs. 22.8%; p<0.001), acute kidney injury (10.7% vs. 1.1%; p=0.012), a small-for-gestational-age neonate (26.1% vs. 23.2%; p=0.015), lower birthweight [2020gr (1062-3100) vs. 2890gr (2510-3200); p=0.026], and a composite of adverse maternal outcome (69.6% vs. 28.3%; p<0.001). The best predictive model according to Akaike information criterion (AIC) and Bayesian information criteria (BIC) criterion comprised sFlt-1 MoMs, HDP, ALT values, MAP, and sFlt/PI GF ratio. After adjusting for each other, sFlt-1 MoM (OR 5.13; 95%CI 2.19-12.05; p<0.001), HDP (OR 32.76; 95%CI 5.24-205; p<0.001), the interaction between sFlt-1 MoM/HDP (OR 0.28; 95%CI 0.11-0.70; p=0.006), and MAP (OR 0.96; 95%CI 0.92-0.99; p=0.030) where the only significant predictors of a composite of adverse maternal outcomes (Naeguellerke R2: 0.42). Predictive probabilities of an adverse maternal outcome showed that women with an HDP have higher probabilities of an adverse maternal outcome despite sFlt-1 levels, however, in women without HDP higher levels of sFlt-1 were independently associated with an increased probability of an adverse maternal outcome.

Conclusion
The main finding of this study is that sFlt-1 is an independent predictor of adverse maternal outcome after adjusting for confounders, and our results demonstrated a sFlt-1 upregulation in patients with PE and SARS-CoV-2 infection, and higher levels among those with help syndrome, eclampsia, and acute kidney injury.