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An Artificial Neural Network model for severe COVID-19 prediction in pregnant women

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Objective

The aim of this study is to develop and validate an ANN model using clinical, angiogenic, and biochemical data that allows the early prediction of the evolution of mild to severe COVID-19 in pregnant women.

Methods

This is a prospective cohort study at the Instituto Nacional de Perinatologia and the Hospital General de Mexico, both third reference hospitals in Mexico City. Inclusion criteria were all pregnant women who arrived at the emergency department with respiratory symptoms and positive RT-qPCR test for SARS CoV-2 between December 2020 and December 2021. Data were collected from the medical record: maternal age, pregestational body mass index, gestational age, pregestational diabetes, chronic hypertension, pneumonia, viral sepsis, acute renal failure, organ dysfunction, ICU admission, intubation, and mortality. Blood samples were routinely obtained at hospital admission, hematic biometry, sFlt-1, PlGF, and biochemical laboratory results were recorded. The primary outcome was pregnant women who developed severe pneumonia defined according to the American Society Criteria. Secondary outcomes were ICU admission, decided according to the Quick Sequential Organ Failure Assessment (qSOFA) score; viral sepsis was defined according to the Sepsis-3 International Consensus associated with SARS-CoV-2 infection and maternal death as a direct result of SARS-CoV-2 infection. The architecture of the ANN model consisted of an input layer of maternal features, a hidden layer with activation functions, and an output layer, the prediction of severe COVID-19 in pregnant women (codified as a binary category 0 or 1, y/n). Layers are connected through weights and biases (coefficients), which allow the model to be adjusted. Maternal input variables included data from four categories: 1) antropometric data including age (years), p-BMI (Kg/m2), gestational age (GA, weeks), and comorbidities such as gestational diabetes (y/n), chronic hypertension, and (y/n)chronic renal disease (y/n); b) clinical data including blood group (O, A, AB, and B), systolic arterial pressure (SAP, mmHg), diastolic arterial pressure (DAP, mmHg), Mean arterial pressure, (MAP, mmHg), MoM IP Aut, MoMPAM, blood oxygen saturation (SpO2, %); c) blood panel profile including D-dimer (ng/ml), troponine (mg/dL), procalcitonine (mg/dL), triglycerides (mg/dL), total cholesterol (mg/dL), C-RP (mg/dL), MoM PlGF, MoM sFlt-1, sFlt-1/PlGF ratio, and d) blood count including leukocytes (x10/L), neutrophils (x10/L), lymphocytes (x10/L), and platelets (x10/L), and days since symptoms presented before hospital admission (days). Input features were normalized between 0.1 and 0.9. The dataset was randomly divided into learning (75%) and validation/test (25%). Five-fold cross-validation was used to minimize overfitting. Back-propagation neural networks (BPNNs) were utilized for training and validating the models using the Levenberg-Marquardt algorithm with Matlab software (R2021b, Natick, MS, USA) and the Deep Learning Toolbox. The performance for cross-validation and validation/test were evaluated with three metrics: the Root Mean Square Error (RMSE, set to 10-36), the correlation and determination coefficients of the linear regression between the experimental and the simulated data (R and R2), as well as the statistical slope and intercept test. This test compares the simulated and actual values (experimental values) obtained from the linear regression with a student t-test analysis. The slope and intercept range must be close to 1 and zero, respectively, with a 95% confidence level. Several activation functions were tested in the hidden layer and output layers (purelin, TANSIG, LOGSIG). The program was run 30,000 times with 100 iterations by each neuron. Input variables were classified through a sensitivity analysis based on weights using the Garson Equation and shown as a percentage.

Results

Ninety-eight COVID-19 positive pregnant women were studied, 29 (30%) women developed severe COVID-19, including 4 (13.8%) maternal deaths. Differences were observed in Gestational age at diagnosis (36.1 vs. 30.3; p=0.001), SpO2% (95.0 vs. 92.0; p=0.009) and Gestational age at delivery (38.0 vs. 33.0; p<0.001) between study groups. Among 29 severe COVID-19 cases, 6.90% of women smoked, 58.6% were admitted to ICU, 13.8% and 17.2% developed an acute renal disease and viral sepsis, respectively. Severe COVID-19 pregnant women had significantly increased leukocytes [9.8 (7.75-14.5) vs. 8.6 (7.05-10.1); p=0.031], neutrophils [8.4 (6.65-12.4) vs. 6.4 (5.4-7.77); p=0.002], and lymphocytes [0.90 (0.50-1.20) vs. 1.3 (1.0-1.6); p<0.001]. Concerning biochemical markers in this group we observed significantly higher levels of glucose [87 (74-120) vs. 77 (73-85); p=0.007], fibrinogen [580 (491-659) vs. 549 (484-583); p=0.045], PT [10.5 (10.1-11.0) vs. 10.9 (10.6-11.4); p=0.014], C-RP [107 (55.8-180) vs. 24.1 (7.76-78.6); p<0.001], procalcitonin [0.34 (0.19-0.68) vs. 0.07 (0.03-0.26); p<0.001], troponin [2.7 (1.25-3.8) vs. 1.52 (0.60-3.44); p=0.020], sFlt-1 concentrations [4050 (2175-10589) vs. 1978 (1152-4638); p=0.005], and sFlt-1 MoMs [1.91 (0.77-5.02) vs. 0.79 (0.56-1.55); p=0.001]. Interestingly, severe COVID-19 pregnant women have significantly low levels of total cholesterol [154 (127-190) vs. 206 (178-236); p<0.001). An initial ANN model was implemented with 27 maternal anthropometric, clinical, and biochemical features on the admission of pregnant women to classify the individual contribution of parameters to the prediction of severe COVID-19 outcome. The results of this analysis showed that age, MoM PAM, MoM IP Aut, neutrophils, lymphocytes, platelets, total cholesterol, troponin, MoM PlGF, MoM sFlt-1 were the most important input variables in severity prediction We then conducted a first input selection process, considering variables associated with COVID-19 severity. Twelve input variables were included: age, comorbidities (including diabetes, chronic hypertension, and p-BMI), mean arterial pressure adjusted for gestational age, neutrophils, lymphocytes, platelets, total cholesterol, troponin, MoM PlGF, and MoM sFlt-1. In the internal validation, the model showed good performance in training and testing with an R2 of 0.926 between the real data and the values estimated by the model. In predicting whether pregnant women at admission will be diagnosed with severe COVID-19, the model showed an area under the curve (AUC) of 0.714 (95% confidence interval [CI], 0.430–0.998) with a sensitivity of 57.1%, a specificity of 100%, an F1-score of 72.7%, a PPV of 100% and NPV of 75%.

Conclusion

The implementation of ANN models using clinical and biochemical data in COVID-19 pregnant women allows prediction of the evolution of C0VID-19 severe form. The early prediction would allow clinicians to implement strategies that could modify the outcome of severe COVID-19.