VALIDATION OF A SEVERITY SCORE TO IDENTIFY PATIENTS ADMITTED FOR COVID-19 PNEUMONIA AT HIGH RISK FOR AN INTENSIVE APPROACH

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INTRODUCTION

The outbreak of the coronavirus disease 2019 (COVID-19), first merged in China in December 2019, is now becoming a Public Health Emergency, recently confirmed as a pandemic disease by the World Health Organization (WHO) (1). It has been estimated that the worldwide number of confirmed cases nearly amount to 1 million with more than 40000 deaths (1).

In particular, since February 2020, a rapidly growing number of cases has been identified in Italy; current data reveal a number of infected over 110000 subjects, with more than 13000 deaths and 4000 hospitalization in intensive care units (2).

The clinical picture of ranges from asymptomatic cases, mild upper respiratory tract infections to severe pneumonia with respiratory failure and death (3). In most severe cases, COVID-19 disease may be complicated by acute respiratory distress syndrome (ARDS), septic shock and multiorgan failure (4).

Since now, more than 30 agents have been tested for efficacy against SARS-CoV-2 and safety, with promising but still not conclusive evidences (5).

Therefore, it results fundamental to early identify those subjects who rapidly may worsen their clinical status, often requiring an intensive care unit (ICU) admission.

It has been showed that, mainly in more severe forms of SARS-Cov-2 disease, there is the development of an hyperinflammatory status resembling a cytokine storm syndrome (6), as already reported in SARS patients (7).

A recent study by Haung et al. reported that patients with COVID-19 infection showed high amounts of IL1B, IFN-gamma, IP10 and MCP1, probably linked to activated T-helper1 (Th1) cell responses.

Those requiring ICU admission had higher levels of cytokines than those subjects not requiring ICU admission, thus suggesting that cytokine storm was associated with disease severity (6).

A similarity between cytokine profile of COVID-19 disease and secondary haemophagocytic syndrome (sHLH) has been reported (4). Therefore, it was suggested to screen all patients with severe COVID-19 infection both for hyperinflammatory markers (like ferritin), and the HScore commonly used to generate a probability for diagnosis of sHLH (8), which includes some laboratory parameters like triglycerides, fibrinogen, ferritin, serum aspartate aminostransferase (8).

A recent retrospective analysis on 487 COVID-19 Chinese patients admitted to Hospital, showed that the 49 (10.1%) severe cases at admission, was elderly, more commonly male and had a higher incidence of hypertension. Therefore, the Authors defined a host risk score on the basis of the three risk factors, aimed to assess the intrinsic host susceptibility to develop severe cases of COVID-19. This score was also validated in 15 out of 66 patients with a mild to moderate presentation of disease at admission, who showed a progression of disease during hospital stay within a median follow-up time of 15 days (9).

Another work by Zhou et al. on 191 Chinese COVID-19 patients showed that older age, D-dimer levels greater than 1 μg/mL, and higher SOFA score on admission were associated with higher odds of in-hospital death (10). Moreover, subjects with most severe forms of COVID-19 illness commonly showed high levels of blood IL-6, high-sensitivity cardiac troponin I, lactate dehydrogenase and lymphopenia (10).

Based on our previous experience with a large number of patients affected by pneumonia from Covid19, we have observed that those subjects with a more severe prognosis might have some predictive markers. We intend to verify if these markers can identify those subjects with Covid19 infection who need a more intensive therapy and to find a prognosis score.

Methods

Before starting the study, the protocol will be submitted to and approved by the local Ethical Committees at the Fondazione Policlinico Universitario A. Gemelli IRCCS, Catholic University, Rome, Italy. Before enrollment each subject will sign the informed consent.

Inclusion criteria: subjects of both sexes aged 18 years or older consecutively hospitalized with diagnosis of pneumonia, confirmed by chest imaging, Covid-19 test positive, given informed consent to data collection from the patient.

Exclusion criteria: age lower than 18 years, pregnancy or breast-feeding.

Nasopharyngeal swab samples will be taken for quantitative real-time polymerase chain reaction to make diagnosis of Covid19 (2 repeated tests).

Data collected include time of type of symptoms (cough, fever, dyspnea, conjunctivitis, diarrhea, asthenia, arthralgia) and duration, comorbidities (presence of diabetes, hypertension, cardiovascular disease), PaO2/FiO2 ratio, age, sex, height, weight, triglycerides, complete blood count, D-dimer, lactic acid dehydrogenase (LDH), high-sensitivity C-reactive protein (hs-CRP), albumin, and ferritin. The duration of the follow-up will be 28 days from the patient's hospitalization or until his/her discharge or death.

Primary end-point

The primary end-point is to identify the best predictors of critical coronavirus pneumonia and to realize a simple severity score able to early classify high-risk individuals admitted to Internal Medicine Department for COVID-19 disease, needing an intensive approach.

The evaluated predictors for the score assessment are the following: symptoms duration, type of symptoms (cough, fever and dyspnea), comorbidities (presence of diabetes, hypertension, ischemic heart disease), PaO2/FiO2 ratio, age, sex, body mass index (BMI), triglycerides, white cell count, lymphocyte count, D-dimer, lactic acid dehydrogenase (LDH), high-sensitivity C-reactive protein (hs-CRP), albumin, and ferritin. These parameters were collected at admission.

Sample size calculation

The sample size determination is based on the following considerations:

1) the objective of the study is that of finding the best predictors of severe coronavirus pneumonia outcome;
2) the study sample will be constituted by inpatients cases of COVID-19 admitted to Internal Medicine Department of Fondazione Policlinico A. Gemelli IRCCS;
3) in order to test the predictive ability of the developed score the study sample will be split into a fitting population and a validation population by using the internal/validation/data-splitting method
4) the following rule-of-thumb will be considered: the power for a test of a medium-sized partial correlation between y and a predictor, holding all other predictors constant, is approximately .80 if N = 104 + m, where m is the number of predictors (11).

Starting from the above considerations, and from the hypothesis that about 20 predictors will be evaluated for development of a risk score able to predict the severe coronavirus pneumonia outcome, the population size of the fitting population is set to N = 104+20=124 patients. In the procedure of splitting the data set into a fitting population and a validation population, the 50% of the entire sample will be used for the fitting step and the remaining 50% will be used as a validation population. A sample size of 248 patients will be therefore necessary.

Statistical Analysis

Primary Analysis

The data set will be split into a fitting population and a validation population by using the internal/validation/data-splitting method. The internal/validation/data-splitting method is chosen to limit the possible increase in bias that can occur with other techniques for internal validation such as

Bootstrapping technique if the original study population contains biases. The portion of the population used as fitting population for model development will be chosen randomly. The model will be then tested, in terms of its performance on the remaining validation population. Computation of the C statistic will be used to indicate the discrimination performance of the model. The C statistic represents a measure of the model's performance in terms of the model discrimination ability to separate subjects with different outcomes, and for the logistic model, it is equivalent to the area under the curve of the receiver operating characteristic (ROC) curve associated to the model (12) Values of C between 0.8 and 0.9 will be considered to give an excellent discrimination.

Computation of the probabilities: For each subject, both from the fitting population and the validation population, the probability of the studied outcome will be computed on the basis of the patient's covariate values. Each subject will be therefore characterized by the values of the covariate set, the outcome (coronavirus-severity, 0/1) and by the estimated probability of the outcome.

Computation of the C statistics: For both the fitting and the validation populations, the C statistics will be computed. The accuracy (percentage of true positive and negative on the total subjects) of the prediction model will be also computed.

Procedure repetition: The entire procedure (data splitting, model fitting, probability computation) will be repeated 200 times.

Model fitting onto the whole population: The model will then be fitted using all the original data.

Results analysis: At the end of the procedure, the distribution of different indicators will be computed: for each variable, frequency histograms of the estimated coefficients along with their associated standard errors and levels of significance will be plotted. The importance index of each variable computed from each data splitting and model fitting will be also plotted.

The estimated coefficients from the whole population will be compared with the respective distributions (they should be centred around the estimates obtained on the whole sample); the distribution of the variability of the model coefficients indicates to which extent the results are dependent from the subpopulation used; comparison between the distribution of the C statistic computed on the fitting and the validation sample, along with the distribution of their Delta provide indication of the discrimination power of the model. It is expected that the C statistic is larger for the fitting sample than for the validation sample. A model with a high discrimination power presents small drops in the values of the C statistic when computed on the validation sample with respect to

values computed on the fitting sample for which the values are expected to be larger (C Delta distribution centred around the zero).

On the basis of the obtained results on the full model, the entire procedure is repeated on the subset of the most important variables to test and validate the final reduced model including the most meaningful predictors. Once the model validation is assessed the fitted coefficients used to compute the probability of the outcome on a generic patient will be those obtained from the "reduced model" fitting on the whole population sample.

Secondary analyses

Secondary analyses include the use of other classification procedures to compare results from the primary analysis. One of the classification procedures that will be used to classify patients with severe and non-severe coronavirus pneumonia outcome, on the basis of the collected variables, will be the Partial Least-Squares Discriminant *Analysis* (*PLS-DA*). A cross validation approach will be followed and the optimal model with the optimal number of PLS components will be derived. The Q2 value, the ROC AUC and the derived misclassification error, by the classification Youden criterium, will be used to quantify the classification goodness. A permutation approach, including 1000 random permutations, will be used in order to associate a P level to the obtained Q2 value. Random forest classification procedure, which is based on learning algorithms, will be also tested following the same procedure of splitting the entire sample into a training set and a test set. Univariate analyses studying the association between severity and predictors will be conducting using Chi-Squared tests or Fisher exact tests when appropriate or univariate logistic regression models for quantitative variables. Secondary analyses will have only an explorative purpose.

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