Clinical prediction rules for adverse outcomes in patients with SARS COV-2 infection by the omicron variant

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Abstract

Background. Factors related to an adverse evolution in COVID19 infection are needed for proper decision making. We try to identify factors related to hospitalization, ICU admission, and mortality related to the infection. Methods. Retrospective cohort study of patients with SARS-CoV-2 infection from March 1st 2020 to January 9th 2022. The sample was randomly divided into two subsamples, for the purposes of derivation and validation of the prediction rule, until omicron variant appearance and afterwards, respectively. Data collected for this study included sociodemographic data, baseline comorbidities and treatments, and other background data. Multivariable logistic regression models using Lasso logistic regression were used . Results. In the multivariable models, older age, male, peripheral vascular disease, heart failure, heart disease, cerebrovascular, dementia, liver, kidney, diabetes, hemiplegia, interstitial pulmonary disease, cystic fibrosis, malignant tumors, as well as diuretics and the chronic systemic use of steroids were common predictive factors of death. Similar predictors, except liver disease, plus arterial hypertension, were also related to adverse evolution. Similar predictors to the previous, including liver disease, plus dyslipidemia, inflammatory bowel disease, respiratory diseases, and the basal prescription of NSAIDs, heparin, bronchodilators, or immunosuppressants were related to hospital admission. All risk scores developed had AUCs from 0.79 (hospital admission) to 0.94 (death) in the validation in the omicron sample. Conclusions. We propose three risk scales for adverse outcomes and hospital admission easy to calculate and with high predictive capacity, which also work with the current omicron variant, which can help manage patients in primary, emergency, and hospital care.

INTRODUCTION

The SARS-CoV-2 infection, which began in December 2019 has now become a global pandemic of unpredictable consequences constituting a threat to public health, as well as causing thousands of deaths daily throughout the world.

Many aspects of COVID-19 remain unknown, given the changing nature of the infection and the similarities and differences between the characteristics of the different waves and this has necessitated frequent reappraisal of care planning. Consequently, in order to provide crucial perspectives for care services and develop appropriate health policies, numerous predictive models have been developed[2] which are regularly being updated.

Currently, the prospect is that COVID-19 will not disappear in the short or medium term, despite the vaccination process implemented during 2021-2022. Moreover, constant study is required of the characteristics of the disease and the factors related to an adverse evolution, in order to enable rapid modification of treatments and reorganization of the health system if necessary.

In this paper, we seek to identify factors related to hospitalization, adverse evolution —defined as admission to an ICU or death— and mortality related to the infection and evaluate their performance in the latest variant of SARS-CoV-2, Omicron.

METHODS

This is a retrospective study of a cohort of patients diagnosed with COVID-19 in the Basque Country based on data from the electronic database and health records of the Basque health service, Osakidetza.

All patients included in this study were residents in the Basque Country who had a SARS-CoV-2 infection, laboratory-confirmed by a positive result on the reverse transcriptase-polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or a positive antigen test between March 1, 2020 and January 9, 2022. From March 1, 2020 to July 31, 2020, positive IgM or IgG antibody tests performed due to patients having symptoms suggestive of the disease or having had contact with a positive case were also included in the sample. The first positive from each patient was collected. Only patients aged over 18 years were included. The study protocol was approved by the Ethics Committee of the Basque Country (reference PI2020123). All patient data was kept confidential.

All data on patients under the care of Osakidetza are held in a unified electronic database. Analysts retrieved data from all positive cases detected during the study period, including sociodemographic data; baseline comorbidities (all those included in Charlson's Comorbidity Index[2] plus angina, arrhythmia, arterial hypertension, dyslipidemia, asthma, bronchiectasis, cystic fibrosis, interstitial lung disease, lymphoma, leukemia, coagulopathy, inflammatory bowel disease and gastrointestinal bleeding); baseline treatments (based on the Anatomical, Therapeutic, Chemical [ATC] classification system); other background data related to care provided in hospital or primary care settings, including dates of hospital admission and discharge and whether patients were admitted to an intensive care unit (ICU); and vital status. Comorbidities were identified based on the International Statistical Classification of Diseases and Related Health Problems (ICD) ICD-9 or 10 codes in the patients' records at baseline.

Comorbidities were grouped as follows: cardiovascular diseases (including myocardial infarction, angina, arrhythmia, congestive heart failure, and peripheral vascular disease); cerebrovascular disease, hemiplegia and/or paraplegia; arterial hypertension; dyslipidemia; dementia; interstitial pulmonary disease, cystic fibrosis, respiratory disease (chronic obstructive pulmonary disease [COPD], bronchiectasis, chronic bronchial infection); asthma; liver disease (mild, moderate or severe); diabetes (with/without organ damage); kidney disease; cancer (malignant tumor, metastatic solid tumor, lymphoma); rheumatic disease; peptic ulcer; inflammatory bowel disease; and coagulopathies.

For baseline medication, we selected drugs based on ATC codes. Baseline treatment was defined as any drugs prescribed before diagnosis with SARS-CoV-2 infection and had no end date. Data identifying residents of nursing homes were obtained from the Basque Health Department.

The outcomes used in the study were as follows: 1.- Hospital admission due to COVID-19, defined if admission occurred within 15 days of the patient's testing positive, when the positive test preceded hospitalization, and up to 21 days after admission when the patient tested positive during hospitalization; 2.-Death during the three months following diagnosis or during a hospital admission as defined previously; 3.- Adverse evolution, including death or ICU admission during a hospital admission related to a SARS-CoV-2 infection diagnosis as defined above. All patients were monitored to April 9, 2022. The period from March 1st, 2020 to December 13, 2021 was considered as a sample for model development (hereinafter referred to as the Derivation Data Set), while the period from December 14 to January 9, 2022, corresponding to the Omicron variant wave was used to validate the consistency of the results obtained (hereinafter referred to as the Omicron - Validation

Data Set).

Statistical Analysis

The Derivation Data Set was randomly divided in equal halves. One half (50%) was used for variable selection and estimation of parameters of the prediction model (train) and the other half (50%) was used for internal validation (test). The Omicron Data Set was used for external validation. Descriptive statistics included frequency tables for categorical variables. Patient characteristics were compared between the subsamples (train vs. test and train vs. Omicron) using the Chi-square test.

Given the large sample size (n train = 120,536 and n test = 120,535), we developed the multivariate logistic regression models (1.- Hospital admission; 2.- Death; and 3.- Adverse evolution) using Lasso logistic regression which employs penalized likelihood for parameter estimates and variable selection in the train subsample. In the final models, only factors with $p<0.01$ were retained. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. The discrimination ability of the model was measured by the area under the ROC curve (AUC).

To develop the predictive risk scores for each of the outcomes, we first assigned a weight to each risk predictor variable in relation to the estimated β parameters based on the lasso logistic regression model derived in the train subsample. We then added up the risk weights of all the patient's predictor variables, with higher scores indicating a greater likelihood of event. The predictive accuracy of the risk score was assessed using the AUC in train, test and Omicron samples. Based on the risk score, we categorized the score into four different levels of risk. The optimal thresholds in the continuous risk scores were determined with the catpredi function of the R package CatPredi, using the addfor algorithm which maximizes the AUC for the categorized score. The performance of the risk classification was evaluated by means of the AUC and by studying the probability of event occurrence in each of the risk categories. In addition, the true positive rate (TPR), true negative rate (TNR) and the net benefit (NB), which considers the relative benefits and harms, were computed for each of the risk cut-off points. The model, score and categorized score were all validated in the Omicron sample by means of the AUC. All effects were considered significant at $p<0.01$. All statistical analyses were performed using R© version 4.1.2.

RESULTS

During the study period, 380,089 people tested positive. A flowchart describing patient evolution is shown in Figure 1. The descriptive data of the entire sample is available in online supplementary Table 1.

The variables identified in the multivariable model related to death were greater age; being male; baseline diseases such as peripheral vascular disease, heart failure, heart, cerebrovascular, liver, and kidney disease, dementia, diabetes, hemiplegia, specific lung diseases such as interstitial pulmonary disease and cystic fibrosis; and history of malignant tumors. Among the basal treatments, use of diuretics and chronic systemic steroids were also related to death. We created a score from 0 to 68, with four categories and cut-off points at 23, 33 and 41 points. The AUCs for the categorized score were 0.9381, 0.9383 and 0.9384, in train, test and Omicron samples, respectively (Table 1).

The variables related to adverse evolution identified in the multivariable model were older age; being male; baseline diseases such as, heart failure, heart and cerebrovascular disease, dementia, kidney disease, diabetes, specific lung diseases such as interstitial pulmonary disease; and history of malignant tumors. Among the basal treatments, the use of diuretics and chronic systemic steroids were also related to adverse evolution. We created a score from 0 to 59, with four categories and cut-off points at 14, 21 and 29 points. The AUCs for this model were 0.8789, 0.8717 and 0.8990, in the train, test and Omicron samples, respectively. (Table 2).

Finally, the variables related to hospital admission identified in the multivariable model were older age; being male; baseline diseases such as heart failure, heart, cerebrovascular, liver and kidney disease, arterial hypertension, dyslipidemia, diabetes, specific lung diseases such as interstitial pulmonary disease and cystic fibrosis;HIV; and history of malignant tumors. Among the basal treatments, the use of NSAIDs, heparin,

bronchodilators, immunosuppressants, diuretics and chronic systemic steroids were also related to hospital admission. We created a score from 0 to 54, with four categories and cut-off points at 13, 19, and 26 points. The AUCs of this model were 0.7879, 0.7852 and 0.7968, in the train, test and Omicron samples, respectively. (Table 3).

For all different models and cut points, we estimated the sensitivity, specificity and Net Benefit percentages (Table 4) while the risk/probability of event was represented for each outcome and risk category (Figure 2).

DISCUSSION

This study, which included a very large cohort of COVID-19-positive patients (380,089), recruited during almost two years of the pandemic, identified predictors of three different outcomes. It allows us to see a pattern of variables common to all three outcomes, including age, sex, cardio-cerebrovascular diseases, diabetes, kidney and liver disease, tumors, and some more serious specific lung diseases such as interstitial lung disease. Additionally, we found two common treatments to all three outcomes, namely the chronic systemic use of steroids and diuretics.

Most of the above factors have been identified and summarized in previous studies.[21,22] Among the predictors of these three outcomes, we find a number of chronic pathologies identified by different studies such as cardiovascular disease (CVD) and cerebrovascular disease (CVD), as well as diabetes, kidney and liver disease. A history of tumors has also been identified as a predictor.

In the case of CVD, the exact pathophysiology underlying the pre-existing role and poor outcome has yet to be determined. SARS-CoV-2 is believed to infect the heart, vascular tissues, and circulating cells via ACE2 (angiotensin-converting enzyme 2), the host cell receptor for the viral spike protein. However, these patients are at higher risk due to concurrent underlying conditions such as advanced age, hypertension, cardiovascular disorders such as arrhythmia, diabetes, etc. These patients are also at risk of developing cardioembolic events, secondary to viral and bacterial infections or new cerebrovascular events secondary to thrombotic microangiopathy, hypercoagulability leading to macro and microthrombus formation in the vessels, hypoxic injury and blood-brain barrier disruption.Likewise, acute cardiac injury is a common extrapulmonary manifestation of COVID-19 with possible chronic consequences and is more prevalent amongst patients with advanced age, a functionally impaired immune system or high levels of ACE2, or patients with CVD predisposed to COVID-19.

Possible pathogenetic links between diabetes mellitus and COVID-19 include effects on glucose homeostasis, inflammation, altered immune status, and activation of the renin-angiotensin-aldosterone system (RAAS).

In the case of patients with renal disease, most cases of fatality were related to end-stage renal disease (ESRD). This could be partly explained by immune system dysfunction and high frequency of underlying comorbidities such as hypertension, CVD, and diabetes in ESRD patients. The results of two recent meta-analyses reveal a significant association between preexisting CKD and severe COVID-19. CKD has been associated with inflammatory status and impaired immune system, as well as a result of over-expression of ACE2 receptor in the tubular cells of patients with CKD.

Any explanations of the relationship between patients with liver disease and adverse outcomes of COVID-19 infection remain controversial. Some studies have shown that patients with a pre-existing hepatic disease have an increased risk of severe COVID-19 infection and higher mortality, which might be correlated with low platelets and lymphocytes in those patients. This may be due to cirrhosis-associated immune dysfunction. Additionally, it has been postulated that liver impairment in COVID-19 patients could also be drug-related and induced when treating COVID-19 infection.

With regard to cancer patients, some analyses of clinical outcomes in different cancer types indicate that the case fatality rate is higher in lung or hematological cancer than other solid cancers. In any case, the occurrence of severe events and death in cancer patients with COVID-19 appears to be primarily accentuated by age, sex, and coexisting comorbidities.

As for less prevalent diseases such as ILD and cystic fibrosis, fewer studies have been conducted in this field. However, patients with ILD are more susceptible to COVID-19 and experience more severe evolution as compared to those without ILD .

With regard to treatment, chronic or recurrent use of systemic steroids prior to SARS-CoV-2 infection may be linked to a greater alteration in these patients' immunity.

Dementia appears as a potential risk factor in many studies. Changes in health care delivery may disproportionately affect older adults with ADRD. Patients with dementia have higher vulnerability, which may be due to living conditions in nursing homes, need for intensive caregiver assistance, and to the inability to self-isolate and manage preventative health measures. As hypotheses, the presence of chronic inflammatory conditions or defective immune responses in patients with dementia may increase their vulnerability to infection or reduce their ability to mount effective responses to infection.

Most previous studies have also shown that age and sex (male) are significant risk factors for adverse outcomes. Furthermore, it has been hypothesized that age-related decline and dysregulation of the immune function, i.e., immunosenescence and inflammation, may play an important role in contributing to increased vulnerability to severe COVID-19 outcomes in older adults. Furthermore, circulating sex hormones in men and women could influence susceptibility to COVID-19 infection, as demonstrated in a previous study, since they modulate adaptive and innate immunity responses.

Amongst the strengths of this study are the enormous sample size, which includes all epidemics and patients in our region up to the beginning of this year, and validation of the models in the wave of the more recent and less severe Omicron variant. In developing all predictive models, we followed the standards of the TRIPOD guidelines. The three models are based on variables that are easy to obtain in any setting, easy to calculate and provide a quick prediction of the patient's risk. Though different prediction models have been proposed, to the best of our knowledge this is the first model that has been validated in Omicron-infected patients. As a practical proposal, patients with low scores (low or moderate classes for death or adverse evolution) can safely stay at home, while those in very high classes should be seen at a hospital level and more intensive care should be considered. In any case, the clinical judgment for each individual patient should prevail. Regarding the limitations, our data is limited to baseline diseases and treatments plus sociodemographic data, without subsequent clinical follow-up information on those admitted. It was decided to proceed in this way in order to select the information we believed to be most reliable and easiest to obtain in any setting. Nonetheless, the AUC of all models is very high, even in the case of hospitalized patients, and is replicated in the Omicron sample.

These analyses provide very useful practical tools both in the field of primary care and in emergency and hospital settings for making decisions on follow-up and treatment of these patients, including during the current Omicron wave. This may allow better clinical follow-up and case management.

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