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Predictive model of severity in SARS CoV-2 patients at hospital admission using blood-related parameters

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ABSTRACT

Introduction

Blood test alterations are crucial in SARS CoV-2 (COVID-19) patients. Blood parameters, such as lymphocytes, C reactive protein (CRP), creatinine, lactate dehydrogenase, or D-dimer, are associated with severity and prognosis of SARS CoV-2 patients. This study aims to identify blood-related predictors of severe hospitalization in patients diagnosed with SARS CoV-2.

Methods

Observational retrospective study of all rt-PCR and blood-test positive (at 48 hours of hospitalization) SARS CoV-2 diagnosed inpatients between March-May 2020. Deceased and/or ICU inpatients were considered as severe cases, whereas those patients after hospital discharge were considered as non-severe. Multivariate logistic regression was used to identify predictors of severity, based on bivariate contrast between severe and mild inpatients.

Results

The overall sample comprised 540 patients, with 374 mild cases (69.26%), and 166 severe cases (30.75%). The multivariate logistic regression model for predicting SARS CoV-2 severity included lymphocytes, C reactive protein (CRP), creatinine, total protein levels, glucose and aspartate aminotransferase as predictors, showing an area under the curve (AUC) of 0.895 at a threshold of 0.29, with 81.5% of sensitivity and 81% of specificity.

Discussion

Our results suggest that our predictive model allows identifying and stratifying SARS CoV-2 patients in risk of developing severe medical complications based on blood-test parameters easily measured at hospital admission, improving health-care resources management and distribution.

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INTRODUCTION

The new SARS CoV-2 (COVID-19) emerged in Spain in March 2020, reaching the pandemic peak in the second half of that month, posing a serious challenge to health-care professionals.

The clinical picture features fever, asthenia, and respiratory symptoms such as dyspnea, cough, or more severe complications like pneumonia or adult respiratory distress syndrome. The remarkable activation of coagulation, inflammation, and endothelial session and hypoxia present a key role in the patients' severity, with an 8% of ICU hospitalizations due to ventilatory support demand (1). Mortality estimates of hospitalized patients are around 21% (1).

Clinical laboratory has played a crucial role in this disease, due to blood-test alterations presented by SARS CoV-2 patients: lymphopenia, lactate dehydrogenase (LDH) elevations, D-dimer (DD) or C-reactive protein (CRP) are characteristics of the disease (2,3,4,5), as well as increased ferritin and interleukin-6 (IL6), both inflammatory markers that sound alarm of a more critic prognosis (1,3).

Several studies have shown that blood-test parameters are associated with SARS CoV-2 mortality, such as CRP (5,6,7), presenting a higher sensitivity than other parameters like age, neutrophils and platelets. DD is also associated with an elevated risk of mortality (8), and other mortality predictive models include LDH, lymphocytes, transaminases, or hyperglycemia (9,10,11).

Other blood parameters were less studied at the beginning of the pandemic, but gained relevance over time, such as creatinine. Recent studies showed strong associations between elevated creatinine and a higher mortality risk in SARS CoV-2 patients. Other blood parameters present even more important prognostic capacity, as they proved to be useful to identify those patients who will require more resources and that might be candidates of ICU admission. In a recent meta-analysis, Brando et al. (3) highlighted the importance of hematological alterations in severe patients, with the ferritin being the most relevant biochemical marker of disease progression. In the studies published by Huang (4) and Liu (14) at the beginning of the pandemic, the predictors of ICU admission were leukocytosis, neutrophilia, lymphopenia, DD, LDH, total bilirubin and alanine aminotransferase (ALT). There are studies that established predictive models with different results, but they all highlight the relevance of CRP, LDH (15,16,17,18), lymphocytes, platelets (17,19), IL-6 and DD (20). In the meta-analysis published by Timotius (21), procalcitonin, albumin, CRP, DD, and LDH were identified as relevant predictors of disease severity. However, they also highlight that thresholds for each parameter are not clearly

defined yet, and that more research should be conducted on that regard.

Thus, the main objective of this study is: to establish a predictive model of disease severity based on blood-test clinical parameters in COVID-19 patients diagnosed at first hospitalization. As a secondary objective we also aim at analyzing clinical and blood-test alterations of those patients.

MATERIAL AND METHODS

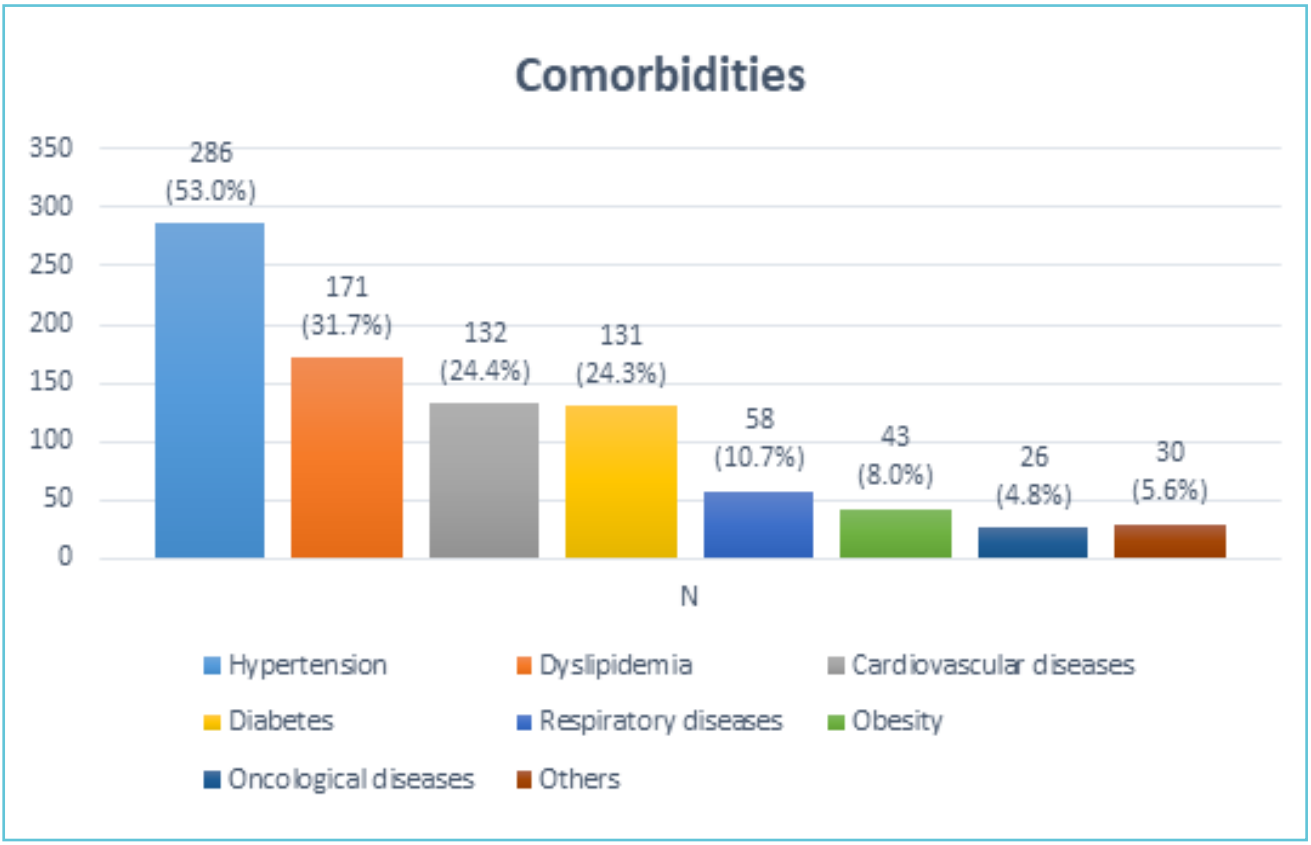
Sample selection

Observational retrospective study. SARS CoV-2 positive patients through rRT-PCR, hospitalized between March 9 and May 9, 2020. Deceased or admitted to ICU patients were considered as severe, and those discharged after hospitalization (not ICU) were considered as non-severe patients. The demographic characteristics collected were: sex, age and comorbidities such as hypertension (HT), diabetes, obesity, dyslipidemia, respiratory, oncological and cardiovascular diseases.

The first blood test of the patient was collected upon admission, always within the first 48 hours after admission.

Hematological variables: leukocytes (x10^3/ µL), lymphocytes (x10^3/ µL), neutrophils (x10^3/ µL), platelets (x10^3/ µL), D-dimer (µg/ mL) and fibrinogen (mg/ dL). Biochemicals: creatinine (mg/ dL), ALT (U/ L), aspartate aminotransferase (AST) (U/ L), creatinine kinase (CK) (U/ L), ferritin (ng/ mL), LDH (U/ L), CRP (mg / L), total proteins (g/ dL), Troponin T (pg/ mL) and total bilirubin (mg/ dL). Hematological parameters were analyzed on an Advia2120 (Siemens®), fibrinogen and D-Dimer on STA-R-Max (Stago®)

Figure 1 Frequency and type of comorbidities in the sample (n and %)



and biochemical parameters on a Cobas 8000 (Roche diagnostics®).

We utilize the most commonly used measurement units in clinical laboratories.

Exclusion criteria:

- Patients without blood-test analysis 48 hours.
- Transfer to another hospital or medical hotel.
- Patients with hematological conditions (due to alteration of the blood count data).
- Patients with hemolyzed samples that could interfere with the results.

Statistical analyses

Statistical analyses were conducted using STATA version 15. The median and interquartile range (IQI), with the method of the weighted average, were used to describe quantitative data. The association between disease severity and comorbidities was assessed using the prevalence ratio.

To test differences between severe and non-severe SARS CoV-2 patients, comparisons were based on the medians, estimating 95% confidence intervals and *p*-values using the Bonett-Price estimation (Bonett and Price, 2002). In the case of troponin T, a comparison of proportions was conducted.

To build the predictive logistic regression model, we first randomly divided the total sample (540 patients) into two parts: 2/3 (360 patients) as a training sample to estimate the model and 1/3 (180 patients) as a validation sample that is subsequently used to assess the reliability of the model. To select the variables to include in the model, a previous screening of the insignificant variables was carried out, based on the results of univariate logistic regressions with a single independent variable. Thus, variables with p values < 0.20 on the univariate regression models were included in the multivariate logistic regression model. We selected the best model from all possible equations, reducing the number of parameters to be included in the equation in order to obtain a more stable model and also facilitate its handling in clinical practice without losing predictive power. To avoid including strongly correlated terms in the model, that might potentially cause stability problems in the estimation algorithm, we discarded parameters that are physiologically and/or pathophysiologically related to each other and provide similar information, keeping only one of them in the equation when it is significant. This is the case of hematological parameters, liver function, kidney function and inflammation/infection. We verify that the final model selected does not violate the assumptions of the logistic regression model. For this, the lineal relationship between the logit and each of the predictors, the absence of collinearity and the absence of distant values and influencing values were evaluated. Outliers were excluded from the analyses, that is, cases with distant values in the predictor variables and cases poorly predicted by the model, detected by residual analysis, and cases with high influence values, detected by three diagnostic indices: DBeta influence index (Hosmer, Taber and Lemeshow, 1991) and the DX2 and DDev indices (Hosmer, Lemeshow and Sturdivant, 2013). Finally, we evaluated its predictive ability by calculating the prediction loss with the validation sample.

RESULTS

The sample comprised a total of 540 patients hospitalized during the first epidemic wave of the SARS-CoV-2 virus during the months of March-April. The age range was from 22 to 99 years and the median age was 68 years with no significant difference between the number

of men (n = 314, 58.15%) and women (n = 226, 41.85%) (p = 0.526).

Regarding disease severity, 374 patients (69.26%) presented mild disease development and a median age of 65 years; and 166 patients (30.74%) presented severe disease with a median age of 75 years. In this last group 155 patients died, which represents a mortality of 28.7% in the overall sample of admitted patients.

Regarding sex, the prevalence of severity in men is 1.21 times higher than in women (95% CI 0.927 to 1.571) (p = 0.158). 78.52% of the patients presented some type of comorbidity. The prevalence of comorbidity is presented below (graph 1).

The probability of greater severity in patients with comorbidities is 33.25%, while the probability of greater severity in patients without comorbidities is 21.55%. The prevalence of greater severity in patients with comorbidities is 1.54 times higher than in patients without comorbidities (95% CI 1.063 to 2.239) (p <0.05).

Table 1 displays descriptive statistics of the blood-test variables and age in both groups studied, median and interquartile range. Table 2 shows the comparison of medians between the two groups: severe vs non-severe, along with its statistically significance.

To build the predictive model of disease severity, we followed the procedure described in the materials and methods section, with the parameters finally estimated (Table 3).

The estimated model equation that predicts the value of the log-odds (logit) of developing severe disease in patients with SARS CoV-2 according to age and laboratory parameters: lymphocyte count, creatinine, total protein, glucose, AST and PCR, is:

Ln O_{severe} = (-9.215265) + 0.1087873 x **Age** (years) - 0.8933988 x **Lymphocytes** (x10^3/ µL) + 0.5728488 x **Creatinine** (mg/ dL) - 0.2791245 x **Total proteins** (g/ dL) + 0.0076588 x **Glucose** (mg/ dL) + 0.01179 x **AST** (U/ L) + 0.0092949 x **CRP** (mg/ L)

To select the optimal cut-off point, we chose the cut-off point p = 0.2859 that maximizes efficiency and corresponds to a sensitivity of 81.5% (95% CI: 70.4 to 89.1) and a specificity of 81.0% (95% CI: 74.6 to 86.2). For the observed prevalence in our sample (27.2%), the positive predictive value is 61.6% and the negative predictive value is 92.2%.

We assessed the significance of the estimated model using the likelihood ratio test. We obtained a result (χ^2 = 111.69; df = 7; p <0.001) that indicates that the estimated model is significant, that is, the set of terms included in the model predicts disease severity in a statistically significant way.

We used the area under the ROC curve (AUC) to assess the predictive ability of the model (AUC = 0.895; exact 95% CI: 0.849 to 0.931), with a prediction loss of less than 5% in the validation sample.

DISCUSSION

Early identification of COVID-19 patients at risk of progressing to severe disease will lead to a better management and more efficient use of medical resources. In this article, we established a predictive model of severity through clinical and blood-test parameters that include age, lymphocytes, creatinine, total proteins, glucose, AST and CRP in the first 48 hours upon admission and that correlate with an increased risk of severe COVID -19 disease.

Regarding the demographic data, a large percentage of patients presented some type of comorbidity (78.5%), but there were no significant differences in disease severity in this regard. Consistent with the SEMI study (1), we observed a large number of patients (52.9%)

Table 1 Descriptive statistics of blood-test parameters and age (n, median, and interquartile range)

	Non-severe disease			Severe disease		
Parameter	**n**	**Median**	**IQI**	**n**	**Median**	**IQI**
Age (years)	374	65	[55; 72]	166	75	[67; 86]
Leukocytes (x10^3 / µL)	374	5.68	[4.608; 7.575]	166	6.765	[4.973; 10.635]
Neutrophils (x10^3 / µL)	374	4.08	[3.048; 5.823]	166	5.3	[3.758; 9.288]
Lymphocytes (x10^3 / µL)	374	1.01	[0.74; 1.34]	166	0.735	[0.498; 1.06]
Neutrophil / lymphocyte ratio	374	4.06	[2.64; 6.25]	166	6.98	[4.57; 13.52]
Platelets (x10^3 / µL)	374	205	[158.5; 257.7]	166	191.5	[153.75; 264.25]
Fibrinogen (mg / dL)	192	590.5	[483; 659.5]	67	663	[469; 741]
D-dimer (µg / mL)	331	0.69	[0.45; 1.17]	137	1.14	[0.72; 2.235]
Glucose (mg / dL)	374	111.5	[101; 134]	166	139	[118; 177]
Creatinine (mg / dL)	374	0.9	[0.8; 1.1]	165	1.2	[0.9; 1.5]
Total bilirubin (mg / dL)	186	0.485	[0.4; 0.51]	77	0.4	[0.4; 0.6]
Aspartate aminotransferase (AST) (IU / L)	187	29	[21; 43]	75	38	[25; 58]
Alanine aminotransferase (ALT) (IU / L)	336	27	[18; 43]	150	26	[17; 44.25]
Lactate dehydrogenase (LDH) (IU / L)	354	280	[226; 347.25]	158	356.5	[274; 501.5]
Creatine kinase (CK) (IU / L)	197	76	[49.5; 127]	68	124.5	[68.5; 321]
Total proteins (g / dL)	185	6.5	[6.2; 6.85]	75	6.3	[5.8; 6.6]
C-reactive protein (CRP) (mg / L)	365	47.8	[21.05; 91.6]	163	115.2	[59.2; 239.4]
Ferritin (ng / mL = µg / L)	213	563	[266; 1212.5]	87	880	[400; 1699]
Troponin T (pg/mL): < 14 ≥ 14	196	138 (70.41%) 58 (29.59%)		65	20 (30.77%) 45 (69.23%)	

Table 2 Median comparison between severe and non-severe patients and statistical significance

Parameter	N	Difference between medians	Confidence interval 95%	*p*-value
Age (years)	540	10	7.199 a 12.801	<0.001
Leukocytes (x10^3 / µL)	540	1.085	0.436 a 1.734	0.0011
Neutrophils (x10^3 / µL)	540	1.22	0.388 a 2.052	0.0041
Lymphocytes (x10^3 / µL)	540	-0.275	-0.368 a -0.182	<0.001
Neutrophil / lymphocyte ratio	540	2.923	1.500 a 4.346	<0.001
Platelets (x10^3 / µL)	540	-13.5	-32.747 a 5.747	0.169
Fibrinogen (mg / dL)	259	72.5	15.655 a 129.345	0.0124
D-dimer (µg / mL)	468	0.45	0.226 a 0.674	<0.001
Glucose (mg / dL)	540	27.5	18.921 a 36.079	<0.001
Creatinine (mg / dL)	539	0.3	0.203 a 0.397	<0.001
Total bilirubin (mg / dL)	263	-0.085	-0.154 a -0.0164	0.0152
Aspartate aminotransferase (AST) (IU / L)	262	9	0.665 a 17.335	0.0343
Alanine aminotransferase (ALT) (IU / L)	486	-1	-5.537 a 3.537	0.666
Lactate dehydrogenase (LDH) (IU / L)	512	76.5	42.185 a 110.815	<0.001
Creatine kinase (CK) (IU / L)	265	48.5	2.337 a 94.663	0.0395
Total proteins (g / dL)	260	-0.2	-0.370 a -0.0300	0.0211
C-reactive protein (CRP) (mg / L)	528	67.4	43.384 a 91.416	<0.001
Ferritin (ng / mL= µg / L)	300	317	-5.264 a 639.264	0.0539

Disease severity	Troponin T (pg/mL)		Total	Proportion	IC 95% (Wilson)	*p*-value
	< 14	≥ 14				
Non-severe	138	58	196	0.296	0.236 a 0.363	<0.001
Severe	20	45	65	0.692	0.572 a 0.791	

Table 3 Parameter estimates from the multivariate logistic regression model to predict disease severity

Severity	Odds Ratio (OR)	CI 95%
Age (years)	1.114925	1.069048 a 1.162772
Lymphocytes (x10^3/ µL)	0.4092624	0.1648353 a 1.01614
Creatinine (mg/ dL)	1.773312	0.8017985 a 3.921976
Total proteins (g/ dL)	0.7564457	0.3590133 a 1.593841
Glucose (mg/ dL)	1.007688	1.000588 a 1.014839
Aspartate aminotransferase (U/ L)	1.01186	0.995918 a 1.028057
C-reactive protein (mg/ L)	1.009338	1.004526 a 1.014174
Intercept	0.0000995	0.000000124 a 0.0798615

presenting hypertension, followed by dyslipidemia (31.7%). On the contrary, our sample had a higher prevalence of diabetes mellitus (24.7% vs 18.7% in the SEMI study) and less obesity (7.9% versus 21.2%).

The proportion of male patients presenting severe illness was higher than the women's (62.6% and 37.36%, respectively), but the differences were not statistically significant. It is worth highlighting the role of age, with a statistically significant difference of 10 years between the patients presenting severe (median 75) and non-severe (median 65) disease. These results are consistent with different studies evidencing positive associations between age and disease severity (5,22), with some of them suggesting the age of 60 years as the cut-off point of severity (22, 7).

Regarding the blood-test parameters, we found significant differences between severe and non-severe patients in leukocytes, neutrophils and lymphocytes, RNL, fibrinogen, d-dimer, glucose, creatinine, total bilirubin, AST, LDH, CK, total proteins and CRP. Similarly, troponin T presents a proportion of values equal to or greater than 14 versus negative troponins, significatively higher in the group with greater severity.

Age and 6 basic biochemical and hematological parameters easily available in any hospital center were included in our final predictive model of disease severity: lymphocytes, CRP, AST, creatinine, glucose, and total proteins. The associations between lymphopenia, elevated CRP and disease severity are widely supported in the literature (15, 16, 17 19, 23). On the other hand, our results show an association with severity in parameters not that studied, such as elevated AST (10) and glucose (11), along with decreased total proteins (24). On the contrary, it is worth noting that other well-studied parameters as ferritin, LDH and D-dimer do not predict severity in our study. In our hospital, a thromboprophylaxis protocol with weight-adjusted low-molecular-weight heparin was quickly implemented

as soon as the patient was admitted, which might be reflected in the D-dimer results.

It should be noted that kidney failure presented an important role as a predictor in the final predictive model, with creatinine showing an Odds ratio of 1,773, data consistent with the studies published by Liang (17) and Torres (23), which show predictive scores of severity and mortality respectively.

The area under the curve of our multivariate logistic regression model, close to 1, indicates that our predictive model allows classifying patients in mild or severe severity based on their age and the above mentioned laboratory analytical parameters. Loss of prediction, less than 5%, indicates that our model is reliable and predicts satisfactorily. At a cut-off point of 0.2859, our model presented a good sensitivity (81.5%) and specificity (81.0%), showing a high negative predictive value of 92.2% for the prevalence of severity in our sample.

To make our results even more sensitive and more specific, we proposed generating a gray area, so that patients with a result < 0.3 would have a high negative predictive value (92.2%), patients with > 0.7 would show a high positive predictive value (86.5%) with a specificity of 97.13%. Patients in the range of (0.3 - 0.7) would be in an intermediate gray zone. If we apply this to our study sample, 20% of the patients would remain in the gray area and giving high sensitivity and specificity to the cut-off points of 0.3 and 0.7. To use this predictive model in other populations or laboratories, we recommend recalculating and adapting these cut-off points to the specific target population.

Our study has several strengths. First, we provide a practical quantitative prediction tool based on just 7 variables, which are inexpensive and easily obtained from routine blood tests. This prediction is conducted at the time of admission, that is, in the first 48 hours after the patient's arrival at the hospital and marks the difference with other predictive studies that do not specify when the analytical variables are collected, which may bias the results. Second, the sample size: we included 540 patients of which 166 present severe disease, thus guaranteeing the robustness of the equation and its validation.

Regarding the limitations, firstly, it is a retrospective study that included all patients at admission, without discriminating whether they were severe or mild at the beginning, secondly, the epidemiological context of the period when the study was conducted may bias the time of analysis when admitting patients with advanced disease and therefore not all patients have the data at the same time of the disease, which can alter our results.

In summary, our data suggest that our predictive model allows in identifying and stratifying COVID-19 patients at risk of severe disease through easily accessible analytical parameters at admission, improving the management and distribution of healthcare resources.

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