Development and validation of a clinical score to estimate progression to severe or critical state in Covid-19 pneumonia hospitalized patients

Francisco Gude
Hospital Clínico Universitario de Santiago de Compostela https://orcid.org/0000-0002-9681-1662
Luis Valdés
Hospital Clínico Universitario de Santiago de Compostela
Lucía Ferreiro (lferfer7@gmail.com)
Hospital Clínico Universitario de Santiago de Compostela https://orcid.org/0000-0002-9023-0429

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Abstract

The prognosis of a patient with Covid-19 pneumonia is uncertain. Our objective was to establish a predictive model of disease progression to facilitate early decision-making.

A retrospective study was performed of patients admitted with Covid-19 pneumonia, classified as severe (admission to the intensive care unit, mechanic invasive ventilation, or death) or non-severe. A predictive model based on clinical, analytical, and radiological parameters was built. The probability of progression to severe disease was estimated by logistic regression analysis. Calibration and discrimination (receiver operating characteristics curves and AUC) were assessed to determine model performance.

During the study period 1,152 patients presented with Covid-19 infection, of whom 229 (19.9%) were admitted for pneumonia. During hospitalization, 51 (22.3%) progressed to severe disease, of whom 26 required ICU care (11.4); 17 (7.4%) underwent invasive mechanical ventilation, and 32 (14%) died of any cause. Five predictors determined within 24 hours of admission were identified: Diabetes, Age, Lymphocyte count, SaO_2, and pH (DALSH score). The prediction model showed a good clinical performance, including discrimination (AUC 0.87 CI 0.81, 0.92) and calibration (Brier score = 0.11). In total, 0%, 12%, and 50% of patients with severity risk scores ≤5%, 6-25%, and >25% exhibited disease progression, respectively.

A simple risk score based on five factors predicts disease progression and facilitates early decision-making according to prognosis.

Introduction

The first cases of pneumonia of unknown origin were detected in Wuhan (Hubei, China) in early December 2019[1]. On 7 January 2020, Chinese scientists isolated a novel coronavirus that was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2), and the relevant disease was called coronavirus–2019 disease (Covid–19)[2]. Since then, the dramatic increase in cases has posed numerous challenges to even the most sophisticated and advanced health systems, which led the World Health Organization (WHO) to declare the outbreak a pandemic in March 2020[3]. To date, health systems worldwide have experienced an exponential increase in hospitalizations and admissions to intensive care units (ICUs) associated with Covid–19[4].

Covid–19 can cause a wide variety of symptoms ranging from asymptomatic infection to life-threatening complications such as acute respiratory distress, multi-organic failure, and death[1,5–7]. Some studies have evidenced that older patients with comorbidities (including arterial hypertension, cardio-respiratory disease or diabetes)[6] and patients with more elevated levels of cytokines in blood[1] are the ones at a higher risk for experiencing severe complications[8,9].

At this time, there are no specific vaccines or treatments for Covid–19. Accurate diagnosis and prognosis of the disease are crucial to alleviating the burden on the health system while the best care possible is provided to patients. A predictive model that combines several variables or parameters to estimate the risk for a poor outcome would help the clinician to estimate the prognosis of patients when limited healthcare resources

are available. Thus, early identification of patients at risk of serious complications is clinically relevant[10]. A recent systematic literature review found ten prognostic models for predicting mortality or progression to severe disease, but only a study involved patients from countries other than China, and all studies had been categorized as being at a high risk of bias[11].

Therefore, the aim of this study was to develop and validate a prognostic model to identify inpatients with Covid–19 pneumonia at a greater risk for developing severe/critical complications, including death.

Methods

Source of data

Data were collected from the medical reports of patients diagnosed with Covid-19 and admitted to the Complejo Hospitalario Universitario of Santiago de Compostela in Spain, a hospital with over 1000 beds, from March 12, 2020 (date of first Covid-19 diagnosis) to April 11. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of good clinical practice and was approved by the Institutional Review Board (IRB) of the Galician Health Service on April 3, 2020 (#2020/194). Informed consent forms were waived by the IRB.

A confirmed case of Covid-19 was defined as a positive result in the reverse transcription polymerase chain reaction (RT-PCR) test on samples obtained from nasal or throat swabs performed in accordance with WHO protocol[12]. Only laboratory-confirmed cases were considered for analysis. Patients with uncomplicated disease, with symptoms of upper airway infection, headache, myalgia, anosmia, dysgeusia or anorexia, but with an SaO_2 >95% and a respiratory rate <25 breaths/minute, all considered as low-risk (<60 years of age and without comorbidities), and high-risk patients (>60 years and comorbidities) were monitored as follows: 1) At home by the TELEA system, a home monitoring platform that allows to monitor respiratory and heart rate, temperature, and SaO_2; 2) patients without an Internet connection at home were monitored via 2-3 telephone calls daily. If the clinical status of the patient deteriorated, a physician contacted them to decide where hospitalization was required or not; 3) previously-institutionalized patients or those without enough assistance at home were transferred to a socio-health center adapted as a hospital. All patients diagnosed with Covid-19 pneumonia were hospitalized.

All patients with Covid-19 pneumonia were eligible for inclusion. Pneumonia was defined as an acute respiratory disorder characterized by cough, at least a novel condensation on chest X-ray and fever for four days or more or dyspnea/tachypnea[13]. Exclusion criteria were simultaneous infection by another germ or in other organ. Fever was defined as an axillary temperature ≥37.5ºC. Diagnosis of acute respiratory distress syndrome (ARDS) was established in accordance by the Berlin definition[14].

The data extracted from the medical history of patients included symptoms, clinical signs, and laboratory test and radiological results at admission (+1 day). The comorbidities considered were arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, other respiratory diseases, kidney and liver disease, heart failure, ischemic heart disease, heart valve surgery, active neoplasm, systemic disease, and

psoriasis. Previous use of drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, statins, corticosteroids, immunosuppressants, antiplatelet agents, and anticoagulants were recorded. The totality of laboratory tests were performed as a function of the clinical care needs of the patients. Determinations in blood included a complete hemogram, coagulation tests (including D-dimer), an evaluation of liver and kidney function, and determination of electrolytes, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), creatine kinase, ferritin, and interleukin 6. Covid-19 was considered severe and the patient was candidate to ICU admission if required mechanical ventilation or had a fraction of inspired oxygen (FiO_2) of at least 60% or more[15]. Radiological anomalies were collected from reports of the Unit of Radiology.

Outcomes of interest were death from any cause, use of mechanic invasive ventilation, or ICU stay.

Statistical analysis

Multiple imputation was used to impute missing data by creating 100 datasets. Missing values were predicted on the basis of all other predictors considered for assessing outcomes[16]. For each of them, 250 bootstrap datasets were generated, and backwards feature selection with the Akaike Information Criterion was performed on every set[17].

The predictors returned by this procedure in 70% of datasets were selected for the final model, and their regression coefficients were calculated according to “Rubin's Rules”[18]. We also studied the possible nonlinear effect of each predictor on the outcome by means of Generalized Additive models (GAM) using splines[17]. Results are presented as Odds Ratio (OR) with 95% confidence intervals (CI). The Nagelkerke R^2 was used to calculate the proportion of variance in clinical outcomes that could be explained by the selected predictors. The different aspects of model performance were studied, including calibration and discrimination[19]. Calibration was assessed using the Brier score, and by plotting the non-parametric estimate of the association between the observed frequencies and the predicted probabilities. The receiver operating characteristics (ROC) curves (and the correspondent area under the ROC curve-AUC) were calculated to test for discrimination. To correct optimism, internal validation was performed using the bootstrap procedure. The procedure was repeated in each imputed dataset, and the average estimates for the AUC, the Brier Score, and the Nagelkerke R^2 were extracted to assess discrimination, calibration, and overall fit, respectively[20]. The final model was selected to derive a score for clinical use and a nomogram was created. Criteria for this selection included both discriminant ability (defined by the AUC) and model simplicity. All statistical analyses were carried out in R version 3.5.1 using the mice rms and psfmi packages). These packages are freely available at http://cran.r-project.org. The analysis conforms to TRIPOD reporting standards[21].

Results

During the study period, 1,152 patients were infected by Covid-19, of whom 229 (19.9%) were admitted for pneumonia. None of the hospitalized patients were lost to follow-up. During hospitalization, 51 (22.3%)

cases progressed to severe disease (Figure 1), of whom 26 (11.4%) needed intensive care, 17 (7.4%) underwent invasive mechanical ventilation, and 32 (14%) died of any cause. The majority of patients (90%) received antibiotic therapy and hydroxychloroquine, and 83.8% received lopinavir/ritonavir. Additionally, 30% were given systemic glucocorticoids, and 8.3% were administered tocilizumab.

Clinical characteristics

Baseline demographic, clinical, and laboratory data are presented in Table 1. The most common symptoms at onset of illness were cough (77.3%), fever (75.5%), and dyspnea (52.8%). Patients with severe disease were significantly older than those with nonsevere disease and were more likely to have higher systolic blood pressure levels ($p = 0.003$), and lower SaO_2 concentrations ($p < 0.001$). The presence of comorbidities such as diabetes, heart failure, and chronic kidney disease was significantly higher in patients who progressed to severe disease. No statistically significant differences were observed between the two groups in main symptoms, although slightly more patients in the severe group manifested confusion ($p = 0.025$).

Table 1. Clinical characteristics of the study patients

Characteristics	All patients	Severe course		Odds Ratio (95%CI)	*p* value
	Missing (n = 229)	yes (n = 51)	no (n = 178)		
Age, yr	*0* 68 (56, 75)	74 (68, 83)	65 (55, 73)	1.06 (1.03, 1.09)	0.000
Male sex	*0* 139 (60.7)	40 (78.4)	99 (55.6)	2.90 (1.40, 6.02)	0.004
Temperature ≥ 37.5ºC	*1* 82 (36.0)	23 (45.1)	59 (33.3)	1.64 (0.87, 3.10)	0.125
Systolic blood pressure, mmHg	*0* 130 (118, 140)	134 (120, 151)	129 (118, 139)	1.02 (1.01, 1.04)	0.003
Diastolic blood pressure, mmHg	*0* 74 (66, 80)	75 (66, 82)	74 (66, 80)	1.01 (0.98, 1.04)	0.521
Heart rate, beats/min	*1* 83 (74, 94)	86 (74, 96)	81 (75, 91)	1.01 (0.99, 1.04)	0.246
SaO_2	*8* 94 (92, 96)	92 (88, 95)	95 (93, 96)	0.87 (0.81, 0.93)	0.000
Symptoms					
Fever	*0* 177 (77.3)	40 (78.4)	137 (77.0)	1.09 (0.51, 2.31)	0.826
Cough	*0* 173 (75.5)	37 (72.5)	136 (76.4)	0.82 (0.40, 1.65)	0.573
Shortness of breath	*0* 121 (52.8)	34 (66.7)	87 (48.9)	2.09 (1.09, 4.02)	0.027
Thoracic pain	*0* 21 (9.2)	2 (3.9)	19 (10.7)	0.34 (0.08, 1.52)	0.158
Diarrhea	*0* 57 (24.9)	10 (19.6)	47 (26.4)	0.68 (0.32, 1.46)	0.324
Anosmia	*6* 17 (7.4)	2 (4.0)	15 (8.7)	0.44 (0.10, 1.99)	0.285
Dysgeusia	*7* 25 (10.9)	3 (6.0)	22 (12.8)	0.44 (0.12, 1.52)	0.192
Confusion	*0* 9 (3.9)	5 (9.8)	4 (2.2)	4.73 (1.22, 18.3)	0.025
Treatment					
Angiotensin-converting enzyme inhibitors	*0* 21 (9.2)	4 (7.8)	17 (9.6)	0.81 (0.26, 2.51)	0.710
Angiotensin II receptor antagonists	*0* 55 (24.0)	15 (29.4)	40 (22.5)	1.44 (0.72, 2.89)	0.308
Statins	*0* 92 (40.2)	23 (45.1)	69 (38.8)	1.30 (0.69, 2.43)	0.417
Corticosteroids	*0* 19 (8.3)	3 (5.9)	16 (9.0)	0.63 (0.18, 2.26)	0.482
Immunosupressors	*0* 15 (9.6)	1 (2.0)	14 (7.9)	0.23 (0.03, 1.86)	0.166
Anticoagulants	*0* 20 (8.7)	13 (5.5)	7 (3.9)	8.36 (3.12, 22.3)	0.000
Antiplatelet agents	*0* 28 (12.2)	5 (9.8)	23 (12.9)	0.73 (0.26, 2.03)	0.550
Medical history					
Chronic obstructive pulmonary disease	*0* 17 (7.4)	7 (13.7)	10 (5.6)	2.67 (0.96, 7.42)	0.059
Arterial hypertension	*0* 101 (44.1)	27 (52.9)	74 (41.6)	1.58 (0.85, 2.96)	0.151
Diabetes mellitus	*0* 50 (21.8)	24 (47.1)	26 (14.6)	5.20 (2.61, 10.3)	0.000
Chronic renal disease	*0* 21 (9.2)	9 (17.6)	12 (6.7)	2.96 (1.17, 7.50)	0.022
Coronary heart disease	*0* 17 (7.4)	5 (9.8)	12 (6.7)	1.50 (0.50, 4.49)	0.465
Heart failure	*0* 14 (6.1)	10 (19.6)	4 (2.2)	10.6 (3.25, 35.5)	0.000
Cancer		5 (9.8)	7 (3.9)		0.109
Systemic disease		2 (3.9)	17 (9.6)		0.214
Pulmonary disease		10 (19.6)	24 (13.6)		0.288

	0 (5.2) 12			2.66 (0.81, 8.75)	
	0 (8.3) 19			0.39 (0.09, 1.73)	
	1 (14.8) 34			1.55 (0.69, 3.51)	

Data are n (%). 95%CI, 95% Confidence Interval

On admission, patients who progressed to severe disease had a lower baseline lymphocyte and platelet count, lower levels of hemoglobin, and higher levels of neutrophils, serum creatinine, urea, CRP, and interleukin-6 (all p <0.01) (Table 2). Abnormalities on chest X-ray images were detected in all patients. Most than half of patients (57.2%) had bilateral pneumonia (Table 3). The most common findings in patients who progressed to severe disease were bilateral multiple lobular and subsegmental areas of consolidation. Table 3 shows a comparison of gasometric parameters between the two groups by level of severity.

Table 2. Laboratory characteristics of the study patients on admission

Characteristics	All patients	Missing	Severe course yes (n = 51)	Severe course no (n = 178)	Odds Ratio (95%CI)	*p* value
White-cell count, 10³ cells/mm³	57.1 (45.1, 72.4)	*8*	69.7 (51.3, 94.0)	54.4 (44.2, 67.9)	1.02 (1.01, 1.03)	0.002
Lymphocyte count, 10³ cells/mm³	10.1 (6.6, 14.3)	*8*	6.6 (4.6, 8.7)	11.3 (7.7, 15.0)	0.84 (0.77, 0.91)	0.000
Neutrophil count, 10³ cells/mm³	38.8 (29.3, 55.4)	*8*	57.5 (38.3, 76.3)	36.7 (27.8, 50.0)	1.03 (1.01, 1.04)	0.028
Platelet count, 10³ cells/mm³	213 (158, 285)	*8*	183 (132, 227)	227 (173, 291)	1.00 (0.99, 1.00)	0.002
Haemoglobin, g/dL	13.1 (12.1, 14.0)	*9*	12.6 (10.6, 13.8)	13.3 (12.5, 14.0)	0.73 (0.60, 0.89)	0.000
C-reactive protein, mg/dL	6.8 (3.2, 12.8)	*14*	11.7 (5.9, 17.4)	11.3 (12.5, 14.0)	1.12 (1.06, 1.18)	0.313
Procalcitonin, ng/mL	0.12 (0.07, 0.23)	*13*	0.2 (0.1, 0.8)	0.1 (0.1, 0.2)	1.11 (0.91, 1.36)	0.012
Lactate dehydrogenase, U/L	472 (367, 631)	*17*	613 (467, 736)	460 (374, 589)	1.23 (1.05, 1.44)	0.135
Aspartate aminotransferase, UI/L	32 (24, 47)	*14*	36 (27, 52)	31 (23, 45)	1.01 (1.00, 1.02)	0.479
Alanine aminotransferase, UI/L	28 (20, 48)	*10*	27 (20, 43)	29 (20, 49)	1.00 (0.98, 1.01)	0.839
Gamma-glutamil transferase, UI/L	34 (22, 61)	*9*	45 (25, 77)	34 (22, 58)	1.03 (0.79, 1.33)	0.151
Total bilirubin, mg/dL	0.6 (0.5, 0.9)	*10*	0.5 (0.4, 0.8)	0.7 (0.5, 0.9)	0.50 (0.19, 1.29)	0.016
Creatine kinase, UI/L	76 (48, 140)	*31*	129 (84, 253)	66 (45, 107)	1.28 (1.05, 1.56)	0.007
Creatinine, mg/dL	0.8 (0.6, 1.0)	*7*	0.9 (0.7, 1.4)	0.8 (0.7, 1.0)	2.23 (1.24, 4.01)	0.000
Urea, mg/dL	39 (30, 54)	*7*	59 (33, 82)	34 (22, 58)	1.02 (1.01, 1.03)	0.061
D-dimer, ng/mL	671 (414, 1118)	*13*	919 (672, 1550)	38 (30, 48)	1.02 (1.00, 1.04)	0.184
Troponin, ng/mL	0.02 (0.02, 0.02)	*37*	0.02 (0.02, 0.11)	0.02 (0.02, 0.02)	1.10 (0.95, 1.28)	0.054
Prothrombin time, seg	12.5 (11.7, 13.4)	*9*	12.9 (12.0, 14.1)	12.5 (11.7, 13.3)	1.11 (1.00, 1.23)	0.162
APTT, seg	30.6 (28.0, 32.8)	*9*	31.7 (28.0, 35.2)	30.6 (28.1, 32.6)	1.03 (0.99, 1.08)	0.000
Interleukin-6, pg/mL	26.8 (13.5, 57.0)	*62*	78.4 (42.8, 121.2)	20.9 (11.4, 40.7)	1.01 (1.01, 1.02)	

Data are median (IQR). 95%CI, 95% Confidence Interval; APTT, activated partial thromboplastin time

Table 3. Radiological and gasometric characteristics on admission

	All patients	Severe course		Odds Ratio	*p* value
	Missing (n = 229)	yes (n = 51)	no (n = 178)	(95%CI)	
Radiologic	*0*				
Unilateral consolidation	98 (42.8)	12 (23.5)	86 (48.3)	Reference	-
Bilateral consolidation	81 (35.4)	28 (54.9)	53 (29.8)	3.7 (1.7, 8.1)	0.005
Interstitial abnormalities	26 (11.3)	5 (9.8)	21 (11.8)	1.7 (0.5, 5.4)	0.361
Consolidation + interstitial	24 (10.5)	6 (11.8)	18 (10.1)	2.4 (0.8, 7.2)	0.122
Gasometry					
FiO_2	*21* 0.21 (0.21, 0.21)	0.21 (0.21, 0.21)	0.21 (0.21, 0.21)	50 (0.2, 12900)	0.166
pH	*25* 7.46 (7.13, 7.48)	7.47 (7.41, 7.49)	7.46 (7.43, 7.48)	0.57 (0.00, 680)	0.877
$PaCO_2$, mm Hg	*25* 32.6 (29.4, 35.7)	31.3 (28.5, 36.0)	32.8 (30.0, 35.6)	0.97 (0.91, 1.03)	0.347
PaO_2, mm Hg	*25* 67.1 (60.4, 75.6)	60.0 (51.8, 67.8)	69.7 (63.1, 76.5)	0.95 (0.93, 0.98)	0.000
HCO_3-, mmol/L	*25* 23.0 (21.0, 25.0)	22.2 (20.0, 24.1)	23.0 (21.0, 25.0)	0.92 (0.83, 1.02)	0.000
SaO_2, %	*23* 94.0 (91.8, 95.2)	91.4 (86.0, 94.0)	94.0 (92.8, 95.4)	0.85 (0.79, 0.92)	0.000
PaO_2/FiO_2 ratio, mm Hg	*27* 313 (271, 354)	262 (227, 300)	326 (290, 360)	0.99 (0.98, 0.99)	0.001
SaO_2/FiO_2 ratio	*24* 444 (421, 452)	423 (383, 441)	447 (433, 452)	0.99 (0.99, 1.00)	

Data are n (%) or median (IQR). 95%CI, 95% Confidence Interval

Multivariate Prediction Models

A regression model was built based on the aforementioned clinical, laboratory, gasometric, and radiographic data to predict the risk of progression to severe/critical disease. Five predictors were identified: Diabetes, Age, Lymphocyte count, SaO_2, and pH (DALSH score, Nagelkerke R^2 0.45, Table 4). As shown in Figure 2, whereas risk increases linearly with age and decreases as SaO_2 diminishes, the relationship with leukocyte count and pH is not linear.

Table 4. Multivariate logistic regression analysis.

	β	SE(β)	OR (95%CI)	*p* value
Intercept	87.4549			
Diabetes, yes	1.4963	0.4480	4.46 (1.86, 10.74)	0.0008
Age, yr	0.0508	0.0171	1.05 (1.02, 1.09)	0.0030
Lymphocyte count				
rcs (1)	-0.0036	0.0011	see Figure 2	0.0011
rcs (1´)	0.0038	0.0017		0.0017
SaO_2, %	-0.1233	0.0434	0.88 (0.81, 0.96)	0.0046
pH				
rcs (1)	-10.6378	7.7831	see Figure 2	0.1717
rcs (1´)	22.0366	9.5570		0.0212
AUC 0.87	R^2 0.44		Brier score 0.11	
AUC corrected 0.85	R^2 corrected 0.38		Brier score corrected 0.13	

β indicates coefficient; SE, standard error; 95%CI, 95% confidence interval;

rcs, restricted cubic splines (to interpret, see Figure 2); AUC, Area under the ROC curve

The receiver operating characteristic curve for this combination of predictors (Figure 3) confirmed its good clinical performance (AUC 0.87 CI 0.81, 0.92). The AUC was higher than that obtained with the CURB-65 (AUC 0.73 CI 0.68, 0.78). The DALSH score showed an acceptable calibration (Brier score = 0.11, *see supplementary material, Figure 1S*). After correcting optimism by bootstrapping, Nagelkerke R^2, AUC, and Brier score were 0.38, 0.85, and 0.13, respectively.

Figure 2S *(see supplementary material)* illustrates a method to estimate the risk of progression to severe disease based on an overall score calculated by the sum of the individual scores obtained in the five variables of the model.

Table 5 shows the individual score of each of the DALSH predictors. The total score indicates the estimated individual risk of severity of each patient. Scores above 80 points mean a >10% risk of progression to severe disease, which is attained by all patients >70 years with diabetes. If patients also exhibit a SaO_2 ≤90%, the risk raises to 20%; if patients also have a ≤1,000 lymphocyte count, the risk of progression to severe disease reaches 50%. As many as 30% of patients (69) had a ≤5% risk of progression (arbitrarily considered as low risk); 89 (39%) had a risk of 6-25% (intermediate risk), and 71 patients (31%) had a >25% risk (high risk). No patients with a DALSH score <66 points (low risk) progressed to severe disease (ICU admission, need for invasive mechanical ventilation, or death); whereas 12% of patients with a DALSH score of 66-100 points (intermediate risk) progressed to severe disease; finally, 50% of patients with a DALSH score >100 points progressed to severe disease. Half of patients identified as high-risk had a mean age of 74 years. Notably, low-risk patients had a mean age of 54 years and none had diabetes.

Table 5. The DALSH score calculation

DM	Points	Age, yr	Points	Lymphocytes, n	Points	SaO_2, %	Points	pH	Points	Total points	Severity risk	Levels
No	0	20	0	150	62	60	100	7.30	24	18	0.005	Low
Yes	31	30	10	250	55	65	86	7.35	15	32	0.010	
		40	20	500	39	70	73	7.40	5	66	0.050	
		50	30	750	23	75	59	7.45	0	81	0.100	Medium
		60	40	1000	10	80	46	7.50	14	101	0.250	
		70	50	1500	0	85	32	7.55	37	125	0.500	High
		80	59	2000	1	90	19	7.60	60	142	0.700	
		90	69	3000	7	95	8	7.65	82	170	0.900	
		100	79	4000	13	100	0			185	0.950	
		110	89							218	0.990	

DALSH, **d**iabetes, **a**ge, **l**ymphocytes, **s**aturation, p**H**; DM, diabetes mellitus; yr, years

Discussion

Given the high transmission rate, potential severity of symptoms, and scarcity of resources that may result from the Covid-19 pandemic, predicting the course of coronavirus is crucial to guaranteeing that patients receive the best care possible. In this study we derived and validated a clinical prediction rule for the prognosis of hospitalized patients with Covid-19 pneumonia. Our results also show that the presence of diabetes, advanced age, lymphopenia, hypoxemia and pH alterations on admission were all associated with disease severity.

The course of Covid-19 pneumonia is uncertain and may lead to death. Predicting the course of Covid-19 pneumonia at 24 hours of admission based on clinical data is challenging but crucial. In a large number of cases, the disease can be controlled by closely monitoring the patient, but severely-ill patients will need aggressive treatment and intensive care. Predicting the course of the disease will enable the early adoption of a management approach in line with the estimated prognosis.

A multiplicity of studies have demonstrated that age is a relevant predictor of progression and mortality[5,7,22,23], which is confirmed by the results of this study (OR 1.06 CI 1.03, 1.09; p=0.000). This may be explained by age-related effects on T- and B-cell function and the excessive production of type 2 cytokines. These alterations impair the body's ability to control viral replication and prolonged inflammatory response, thereby resulting in disease progression[24].

Pneumonia may induce ischemia, endothelial dysfunction, and alterations in atherosclerotic plaques, which increases the short-term risk of cardiovascular events, especially in patients with previously known cardiovascular disease[25]. This may explain the fact that some studies –but not all[1]– have revealed a relationship between previous cardiovascular disease and a poorer prognosis of Covid-19[5,7,22]. In our study, patients with a previous diagnosis of heart failure were very likely to have a bad prognosis (OR 10.6 CI 3.25, 35.5; p=0.000). Nevertheless, a relationship was not observed with ischemic heart disease. A variety of studies have established a relationship between diabetes and disease progression[5,7,22,23,26]. In our case, Covid-19 pneumonia was five-fold more likely to progress to severe disease in patients with diabetes (OR 5.20 CI 2.61, 10.35; p=0.000). However, no studies have been conducted to date to clarify the relationship between diabetes and Covid-19.

Although prognosis is favourable in most patients, those with Covid-19 pneumonia can develop dyspnea and hypoxemia. The underlying pathophysiology of disease progression seems to be that of severe ARDS. In these cases, the activation of alveolar macrophages by Covid-19 may trigger the release of powerful proinflammatory mediators and chemokines, the accumulation of neutrophils and monocytes, and the production of toxic mediators, which would lead to a loss of alveolar endothelial and epithelial barrier function, and ultimately induce alveolar and interstitial edema[27]. Analytical alterations identified in critical patients with Covid-19 pneumonia could be associated with adverse ARDS outcomes. This suggests that infection could induce cell-mediated immunity alterations, the activation of coagulation, and myocardial, hepatic or renal damage. In line with other publications, our study demonstrates that the risk of disease progression increases with alterations in SaO_2[7] (OR 0.85 CI 0.79, 0.92; p=0.000); LDH[5,6,7,9,22] (OR 1.23 CI 1.05, 1.44; p=0.012); CRP[6,7,9] (OR 1.12 CI 1.06, 1.18; p=0.000); IL-6[6] (OR 1.01 CI 1.01, 1.02; p=0.000); and

lymphocyte count[5,6,7,9,22] (OR 0.84 CI 0.77, 0.91; p=0.000), which are the most commonly used inflammation markers.

Our prognostic model is based on five predictors: diabetes, age, lymphocyte count, SaO_2 and pH, which we call the DALSH score. This score has demonstrated a good discrimination power (AUC 0.87 CI 0.81, 0.92). The DALSH score may be highly useful in clinical practice as these predictors can be easily determined in most settings and are usually recorded on admission. In addition, this score makes it possible to establish risk levels (even arbitrarily: ≤5%, low; 6-25%, intermediate and >25% high) that may be useful to guide decision-making. Thus, a patient identified as low-risk is unlikely to experience disease progression; a relatively low number of patients identified as intermediate-risk will develop disease progression, and a large proportion of high-risk patients will experience disease progression. The cases observed in our series were 0%, 12% and 50%, respectively. Determination of risk would help clinicians adopt the appropriate therapeutic measures.

Any pH alteration is associated with a higher risk for progression. pH decrease is probably related to hypercapnia secondary to alveolar hypoventilation, whereas its increase may be due to the presence of respiratory alkalosis with progressive hyperventilation caused by hypoxemia. The two settings can co-occur with disease progression (Figure 2D). A decrease in lymphocytes count causes an increase in OR, and the same occurs when it increases, although the effect is more subtle (Figure 2C). A recent systematic literature review on prognostic models for predicting mortality or progression to severe disease revealed that these models have good to excellent performance. However, only a study involved patients from countries other than China, and all studies had been categorized as being at a high risk of bias, mainly because the sample of control patients was not representative, patients who had not experienced the event of interest by the end of the study were excluded; and model overfitting. The performance estimated of these studies were rated to be optimistic and misleading[11]. Unlike some of those studies, in our study all patients were followed-up until discharge or death, and objective predictors were used. A major strength of our study is the high-quality data obtained for all predictors and the minimal rate of missing data.

This study has several limitations. First, since the model was developed in a single population, a major limitation is the lack of external validation. Second, sample size was not large enough to adequately develop a multivariate regression model in which 53 predictors were entered. For this reason, after multivariate analysis, we resampled the development sample using a bootstrapping technique. The purpose was to avoid overfitting and estimate the stability of the dataset. As a result, five variables were retained in the model.

In summary, our study identified five straightforward, objective predictors easily determined on admission, which are associated with progression to severe or critical state in hospitalized patients with Covid-19 pneumonia. A simple risk score based on these factors predicted disease progression and allowed us to adopt therapeutic measures in accordance with patient's prognosis from the very moment of diagnosis. Further studies should be conducted to validate the clinical value of the DALSH score for populations from other geographic areas.

Declarations

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Supplementary Information

Figure S1. Calibration plot for the final model in imputed validation samples. Observed severity disease vs. predicted severity disease. Diagonal line indicates perfect calibration.

Figure S2. Nomogram for prediction to severe disease among COVID-19 patients with pneumonia.

Instructions: Locate the patient's age on the (Age) axis. Draw a line straight upward to the point's axis to determine how many points toward the probability of progression to severe disease the patient receives for his/her Age. Repeat the process for each variable. Sum the points achieved for each of the predictors. Locate the final sum on the Total Points axis. Draw a line straight down to find the patient's probability of having severe disease.

DM = Diabetes Mellitus.

Figures

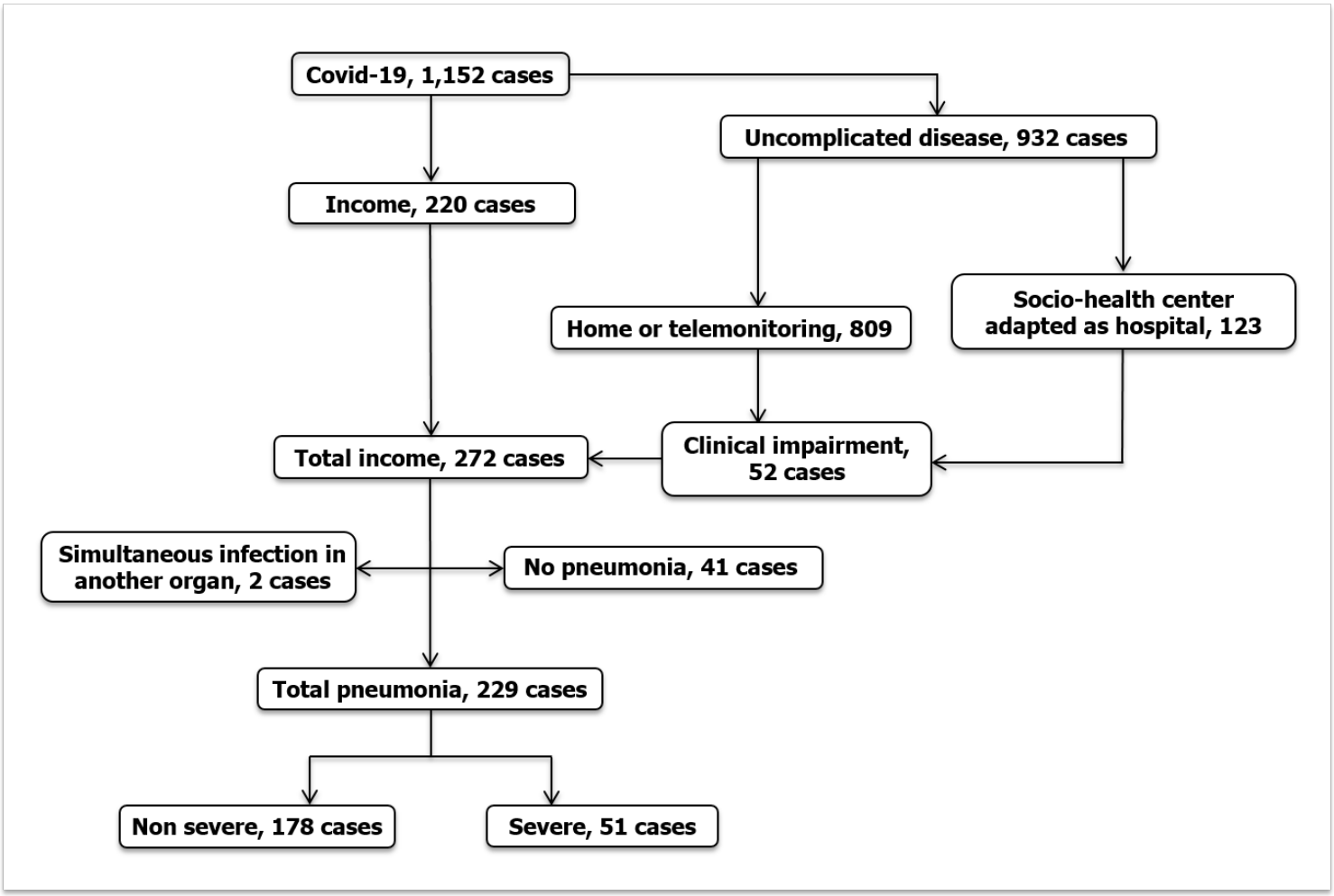

Figure 1

Flow chart for management of patients with Covid-2019 in health area of Santiago de Compostela.

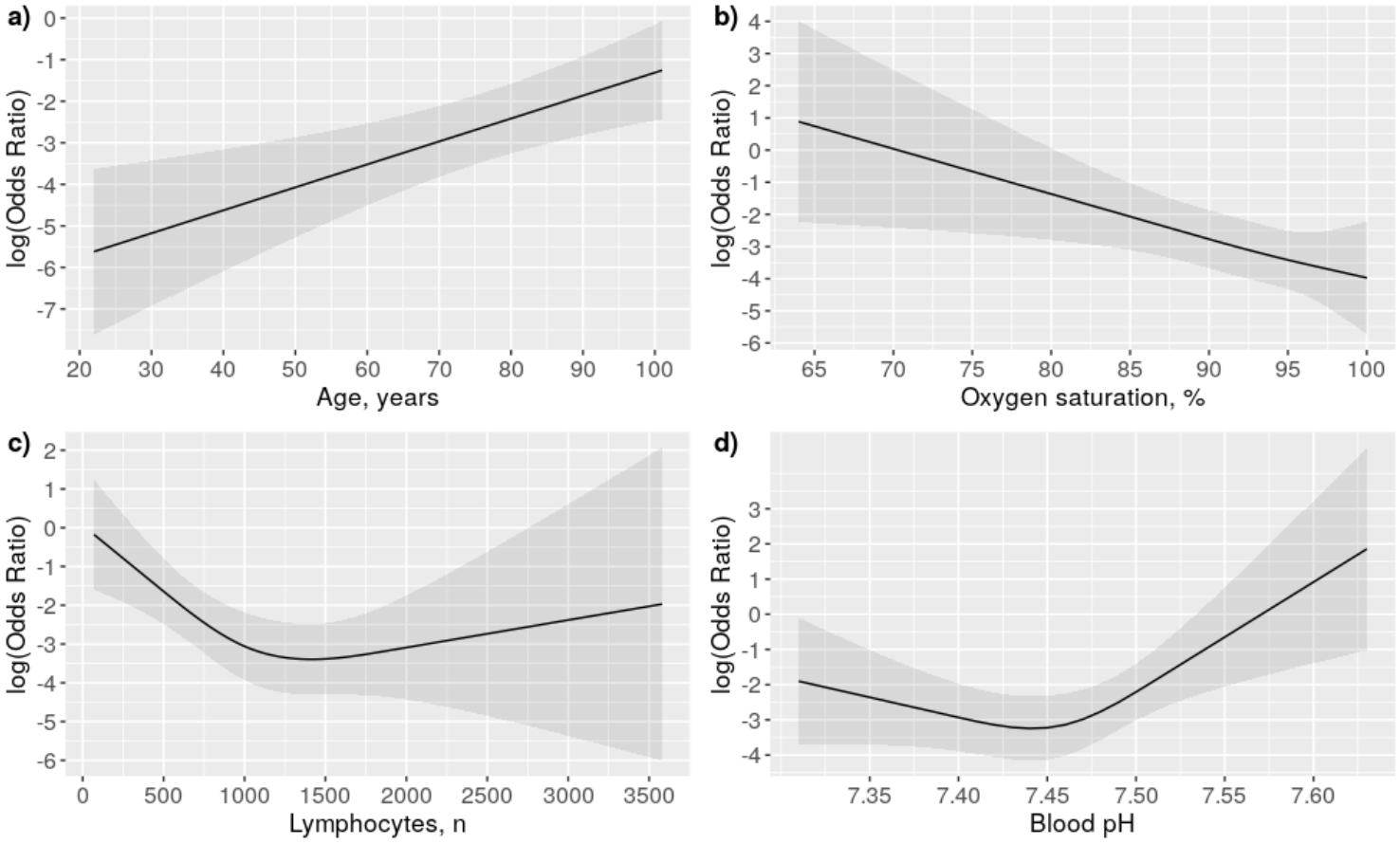

Figure 2

Effects of age, oxygen saturation, lymphocytes and pH on the risk for progression to severe disease.

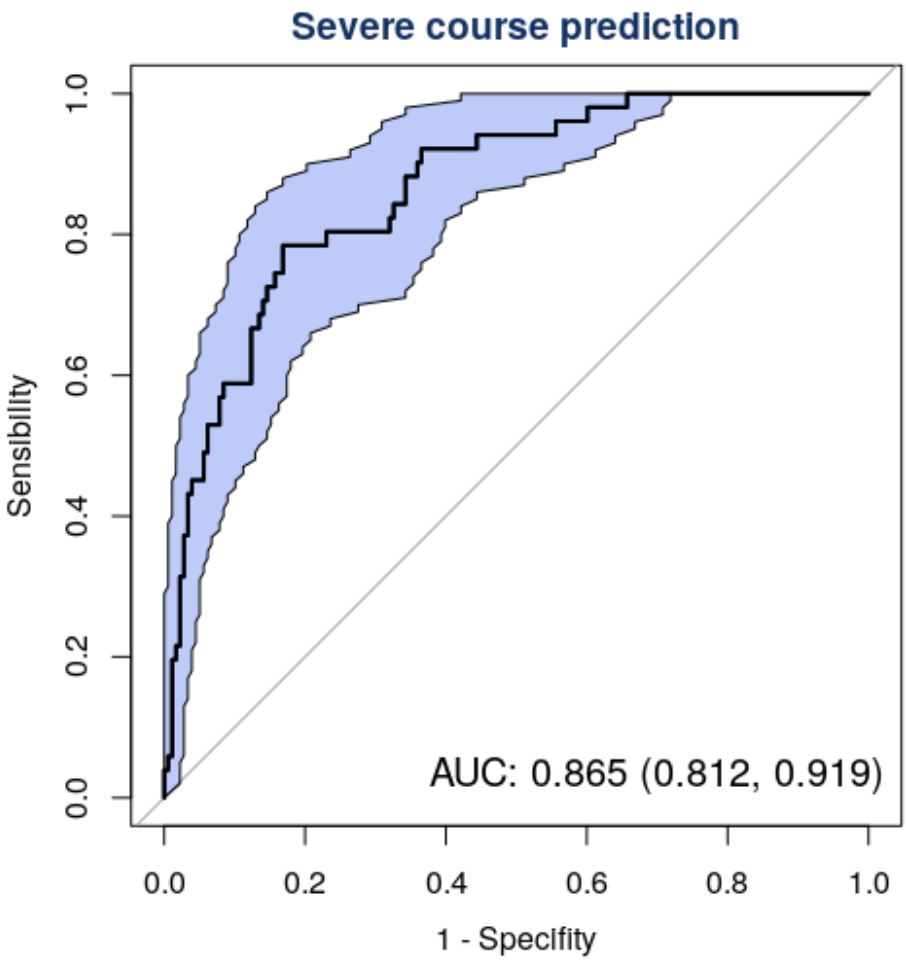

Figure 3

Receiver operating characteristic (ROC) curve for risk of severity in COVID-19 patients with pneumonia. Figures show Area under the Curve [AUC (95% Confidence Interval)].

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Figure1S.tiff
- Figure2S.tiff