Busto COVID-19 Score Identify Low Risk Patients. External Validation.

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Research

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Abstract

Background: Coronavirus disease of 2019 (COVID-19) is associated with severe acute respiratory failure. Early identifcation of low-risk COVID-19 patients is crucial, discharging safely patients to home and optimizing the use of available resources.

Methods: We aimed to external validate a simple score for the prediction of low-risk outcomes. A retrospective cohort study of patients hospitalized for COVID-19 was carried out by the Busto Hospital and Niguarda hospital. Epidemiological, clinical, laboratory, and treatment variables were collected at hospital admission. Variables included in this retrospective cohort were analized to validate the *Busto COVID-19 score* as a Clinical Risk Score able to individuate low risk COVID-19 patients. Among COVID-19 patients admitted to the hospital, severe outcome was defned as the composite of the admission to the Intensive Care Unit or death.

Results: The development cohort included 427 consecutive patients. The mean (SD) age of patients among the cohort was 60.5 years; 273 (63%) were men. As potential predictors, Busto COVID-19 score variables include: lung ultrasound abnormality, age, total white blood cells count , C-reactive protein value, pO2/FiO2 ratio, lactates value, arterial hypertension and fever from 5 days or more and resulted in the best performing score with an area under the curve in the derivation sample of 0.88 and 0.71 in the external sample.

Conclusions: The proposed score can identify patients at low risk for severe outcome who can be safely managed in a low-intensity setting after hospital admission for COVID-19.

Introduction

The first human cases of SARS-CoV-2 were reported in Wuhan, Hubei Province, China in January 2020[1 2]; subsequently, it spread worldwide, officially being defined as a pandemic by WHO on 11 March 2020.[3–5] Italy was the first country outside Asia to be heavily affected by the virus and the Lombardy Region had the highest burden of mortality and strain on its healthcare system.[6] However, a substantial reorganisation of healthcare facilities was necessary in all Italian regions to cope with the widespread and rapid increase in COVID-19 patient flow to emergency departments. Prompt referral to the appropriate care setting (ie, low vs intermediate or high intensity) is of crucial importance to improve outcomes and healthcare resource utilisation.[7–9] Given the high number of patients to be triaged during this emergency and the relative shortage of hospital beds, the availability of a disease-specific mortality risk score since initial triage might have been useful in identifying the appropriate level of care and reducing delay. However, there is a lack of reliable prognostic prediction models and, at present, no tool for the early stratification of mortality risk has been fully identified.[10] A recent systematic review of prediction models concluded that the performance of prognostic estimates for COVID-19 may be overoptimistic and misleading, because of the high risk of bias in patient selection, unclear outcome definition and length of follow-up.[10] Recently, clinical scores to predict the occurrence of critical illness and/or fatal outcome

during COVID-19 were developed in a cohort of Chinese patients belonging to more than 500 centres throughout the country.[11 12] However, these were developed in a specific region which could potentially limit the generalisability of the risk score to other areas of the world. Therefore, the aim of the present study was to external validation a novel COVID-19 in-hospital mortality risk score (hereafter referred to as Busto score), based on data rapidly obtainable soon after hospital admission. To this end, we analysed a consecutive series of COVID-19 patients admitted to one tertiary care hospitals located in Northern Italy.

Methods

A retrospective, observational, multicentre registry of patients hospitalized for COVID-19 in Italian hospitals was designed and promoted by the author. Two centers participating in this registry contributed to the present study, one in Milan and one in Busto Arsizio, Italy. As the registry aimed to record standard local practices, no specifc treatments, tests, or procedures were mandated by the study protocol. All participating centers received approval from the local Ethics Committees. We obtained the medical records and compiled data for 427 consecutive hospitalized patients with laboratory-confirmed COVID-19 from February 28 to June 5 2020. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal-pharyngeal swab specimens[7]. Alternative respiratory specimen collection in the intubated patient included tracheal aspirates and bronchoscopy alveolar lavage. Fever was defined as an axillary temperature of 37.5°C or higher. The arterial oxygen saturation in room air (SpO2) was measured on arrival of the patient in Emergency Room with a CE certified Pulse Oximeter Fingertip and at the same time a blood gas analysis was also performed. The C-reactive protein (PCR, mg/L), Lactate dehydrogenase (LDH, U/L), White blood cell (WBC, 10^3/mm^3) count are routine laboratory tests. The P/F ratio represents the arterial oxygen pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction, not a percentage). The results used in the rule where the Emergency Department (ED) values not the peak values observed during the hospital stay. The ultrasound pattern was carried out in accordance with the use of lung ultrasound for COVID-19 patients proposed by Soldati G et al[19]. We defined “Wet/Interstitial syndrome” pattern when the operator highlighted B lines, pleura line broken and below the breaking point small to large consolidated areas (score 2 and 3); "Dry/Interstitial syndrome" pattern when the pleura line was continuous, regular or indented with visible vertical areas of white below the indent (B lines). B lines reflect local alterations in the acoustical properties of the lung caused by a replacement of air by water, blood, or fibrous tissue[8,9,10]. Besides, if the “Wet pattern” was localized to one segment of one lung, the whole ultrasound pattern in that patient was considered “Wet”.

Laboratory confirmation of SARS-CoV-2 was performed at the Grande Ospedale Metropolitano Niguarda in Milan. RT-PCR assays were performed in accordance with the protocol established by the WHO[7]. We applied the rule described by Foieni et al.[25]. We used clinical variables routinely available at presentation that were previously shown to be associated with mortality in patients with Covid-19 or other acute diseases[11].

STATISTICAL ANALYSIS

Categorical variables are expressed as frequencies and percentage; continuous variables as mean and standard deviation or as medians and interquartile range, as appropriate. A clustering of the scores divided patients into four specific groups (group 1, group 2, group 3, group 4). In order to assess the discriminatory power that the model has to predict outcomes, the study presents a comparison between groups from derivation and external validation sample. In order to assess the reliability of the model regardless of random sampling errors, we performed Independent sample T-Test, comparing the scores mean of each group among our independent samples. Moreover, we got ROC curves to evaluate the area under the curves (AUC) of each sample, considering the outcome “In-hospital mortality” as the state variable. All the analyses have been performed making use of Microsoft Excel 2016 and IBM SPSS Software.

Results

427 patients with COVID-19 were included in the external validation sample. Most patients were men (273-63%), with a mean age of 60.5 years (4-99) and 191 (45%) patients suffered from Arterial Hypertension (Table 1); in both samples, the average value of lactates, the P/F index and LDH was not very different; the CRP value of the derivation sample is higher than the external validation sample (12.8 mg/dL vs 8.2 mg/dL). The weighted variables of the score system are illustrated in Table 2. The prediction rule identified similar populations with a comparable score mean in each of the four groups across the derivation and external validation sample (Table 3). We point out that 2 patients of group 1 were admitted to the ICU; they actually featured a discrepancy between pulmonary ultrasound (dry-interstitial syndrome without consolidations) and thoracic CT (severe interstitial pneumonia with subpleural consolidation). However, we state that in the first group it has not been registered people that died (Figure 2). The rule’s discriminatory power for mortality was similar in the derivation and external validation samples, with an area under the receiver operating characteristic curve (ROC curve) of 0,90 (CI95% 0,801-0,982) and 0,71 (CI95% 0,64-0,78), respectively (Figure 2). The test proved to be not very sensitive but with a high specificity (98%). This can be explained by the fact that in all identified groups there may be patients discharged, but no progression to an unfavorable outcome for the patients who are stratified in group 1.

Table 1
Baseline patient characteristics in the derivation and external validation samples

Patients Characteristics *	**Derivation samples** ***(n=79)***	**External samples** ***(n=427)***
Age (min-max, mean)	31-91 (66.8)	4-99 (60.5)
Male sex (%)	54 (68%)	273 (63%)
Hypertension (%)	56 (70%)	191 (45%)
Temperature >37.5 (%)	65 (82%)	348 (81.4%)
Pulmonary pattern “Wet” (%)	28 (35%)	176 (41.2%)
Respiratory rate (min-max, mean, median)	15-48 (26;24)	12-40 (22;20)
Arterial oxygen saturation (min-max, mean, median)	63-96 (88;88)	54-100 (94;95)
Absolute White blood cell count ($10^3/mm^3$) (min-max, mean, median)	1.1-16.1 (8.06;7.06)	1.51-66.5 (7.64, 6.78)
CRP (mg/L) (min-max, mean, median)	0.1-41 (12.8;11)	0.1-38.60 (8.21, 6.70)
LDH (U/L) (min-max, mean, median)	87-1602 (504;420)	130-677 (336;320)
BMI (kg/m^2) (min-max, mean, median)	18.4-37 (26;26)	16-50 (28;27)
P/F Ratio (min-max, mean, median)	50-460 (243;252)	51-505 (288,304)
Lactates (mg/dL) (min-max, mean, median)	2.3-47.7 (13.78;11)	4.3-87.1(14.18, 11.70)

Note 1. CRP, C-reactive protein; LDH, lactate dehydrogenase; P/F ratio, the arterial oxygen pressure divided by the FIO2 (the fraction of inspired oxygen expressed as a decimal); BMI, Body Mass Index

Table 2
Multivariable predictors of outcomes in the Busto COVID-19 score

Variables	ß-coefficients	95%CI	pValue
Fever for more than 5 days	0,219	-0,15 - 0,59	0,24
Hypertension	0,194	-0,12 - 0,51	0.22
Pattern US “Wet”	0,731	0,42 - 1,03	<0,001
P/F ratio	0,002	0,00 - 0,003	0,02
Lactates (mg/dL)	0,041	0,02 - 0,06	<0,001
WBC (G/L)	-0,022	-0,07 - 0,02	0.36
CRP (mg/dL)	0,019	0,00 – 0,03	0.02
Age	0,014	0,00 – 0,02	0.02

Table 3
Groups based on Busto score applied to external samples

Medical Outcomes	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*Total*
Discharged (outcome 1)	*62*	*115*	*101*	*28*	*306*
Admitted to ICU (outcome 2)	*2**	*30*	*30*	*11*	*73*
Exitus (outcome 3)	*0*	*11*	*21*	*16*	*48*
Total samples	*64*	*156*	*152*	*55*	*427*
* Hight discrepancy between ultrasound (negative) and CT (whit large and bilateral consolidations)					

Table 4
Risk class-specific medical outcomes in the derivation, validation samples and external samples

Medical Outcomes	Derivation sample (n=79)	Validation sample (n=40)	External samples (n=427)	pValue
Discharged	**52 (66% of the sample)**	**30 (75% of the sample)**	**308 (72% of the sample)**	0.47
Group 1	12 (100%)	5 (100%)	62 (97%)	
Group 2	28 (84%)	11 (69%)	115 (73%)	
Group 3	11 (55%)	12 (85%)	101 (66%)	
Group 4	1(7%)	2 (40%)	28 (51%)	
Admittend in ICU	**9 (11% of the sample)**	**4 (10% of the sample)**	**73 (17% of the sample)**	0.44
Group 1	0%	0%	2*(3%)	
Group 2	3 (9%)	3 (18,75%)	30 (19%)	
Group 3	5 (25%)	1 (7%)	30 (20%)	
Group 4	1 (7%)	0%	11 (20%)	
Exitus	**18 (23% of the sample)**	**6 (15% of the sample)**	**48 (11% of the sample)**	0.44
Group 1	0%	0%	0%	
Group 2	2(6%)	2 (12,5%)	11 (7%)	
Group 3	4(20%)	1 (7%)	21 (14%)	
Group 4	12(86%)	3 (60%)	16 (29%)	
* Hight discrepancy between ultrasound (negative) and CT (whit large and bilateral consolidations)				

Discussion

The first and secondary COVID-19 outbreak put high pressure on Lombardy healthcare services. To prioritize resources for patients with the highest risk mortality, we developed a clinical prediction rule for prognosis of COVID-19 patients and a calculator to allow clinicians to calculate the likelihood (with 95% CI) that a hospitalized patient could develop critical illness. The performance of the rule was reliable, but its clinical use involved its validation on an external population. In the derivation and external validation samples, we didn't observe any significant difference between risk groups considering specific mortality, ICU admission and discharge. Our rule accurately identifies patients who are at low risk of fatal medical outcomes: group 1 and group 2 patients respectively had 0.4% and 7% or less admission in ICU, 0% and 2% in-hospital mortality. Our rule can provide clinicians with an explicit tool to identifying low-risk patients

with COVID-19 who might be potential candidates for outpatient treatment or early hospital discharge. Group 4 confirmed a high rate of ICU admissions and mortality rate (20% e 29% respectively). Furthermore, we observed a significant reduction in ICU admissions and mortality in both group 3 and group 4 compared to the previous study of deriving the score[25]. It could likely be the sign of systematic use of the steroid[26,27] and heparin. The intermediate groups (groups 2 and 3) are the most numerous and probably correspond to the overlap subset identified by the Siddiki model[17]. We believe that this is probably the point where an adequate therapeutic approach can interrupt a process that leads to severe hyperinflammatory syndrome. The study produced in China by Zhou et al[31] proposed a predictive model for the severity of COVID-19 using age, neutrophil / lymphocyte ratio, CRP and D-Dimer as variables. The proposed model resulted in a negative predictive value of 0.93, a positive predictive value of 0.41, a specificity of 0.70 and a sensitivity of 0.89. Ageno et al[32] recently produced a 6-variable score (SIMI score) starting from the variables proposed by Zhou with the addition of the anamnestic data of chronic ischemic heart disease (CHD) and the value of alanine aminotransferase (ALT). This retrospective and observational study takes into consideration data from a multicenter registry promoted by the Italian Society of Internal Medicine a database made up of 5 centers in northern Italy. Despite the excellent statistical analysis, the generic variables used not associated with lung imaging leads to an overestimation of an unfavorable outcome. It is not difficult for many COVID-19 patients to reach a value of 7 as the score suggests. Furthermore, this study does not envisage a validation of the score on a dataset outside the register. In a larger study from Liang et al[24] including 1590 patients for the derivation set and 710 patients for the validation set, 10 variables were identified as independent predictive factors for adverse outcome (admission to the Intensive Care Unit, need for invasive ventilation and death). This study developed an online calculator to enter the values of 10 variables including X-ray pattern. Our specific experience allowed us to use, instead of the X-ray pattern, the easier disposable and user-friendly ultrasound tool. Moreover, the Busto Covid-19 score has the advantage of the use of fewer variables, which potentially makes it suitable for daily clinical practice. We also believe that the real challenge in approaching the COVID-19 patient is to identify patients who can be managed in facilities outside the hospital or at home. In this way, hospital resources are preserved for patients with more compromised clinical pictures. The Busto score brings together anamnestic, laboratory and imaging variables and identified a series of patients who could be managed outside the hospital. We suggest a practical tool easy to use even in Emergency Room for risk stratification that classifies patients with COVID-19 at increasing risk of death and other adverse outcomes. It can improve outpatient management and early hospital discharge of patients with COVID-19 identified as low risk (group 1 and group 2) with large cost savings without added risk. The dataset from the Grande Ospedale Metropolitano Niguarda of Milan confirmed the results of our previous experience. This study has some limitations that need to be acknowledged. First, the study was conducted in a single country, and subsequent validation in other geographic areas with different health organizations would be required. Second, given the observational nature of the study, we may have missed other variables that are not routinely tested in these patients on admission and that may also result to be predictive of adverse outcomes. Finally, the clinical impact of this score also needs to be assessed in management studies which randomize patients or centers to the

use of the score or to gestalt. In conclusion, the Busto Covid-19 score identifies COVID-19 patients with low risk of in-hospital mortality and admission to intensive care unit (ICU). Moreover, it establishes an intermediate portion of patients that should be treated accurately to avoid an unfavorable clinical evolution.

Declarations

Author Contributions: F.Foieni, G.Sala and N.Ughi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: F.Foieni, G.Sala, N.Ughi

Acquisition, analysis, or interpretation of data: LM Beltrami, Gaudio F, Menegon V, N. Ughi

Drafting of the manuscript: F.Foieni, G.Sala, LM Beltrami

Critical revision of the manuscript: F.Foieni, P.Ghiringhelli, O.Epis.

Statistical analysis: F. Foieni

Administrative, technical, or material support: LM Beltrami,

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Compliance with ethical standard

Conflict of interest The authors have no conficts of interest to disclose related to this study.

Statements on human and animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent For this type of study formal informed consent was not required.

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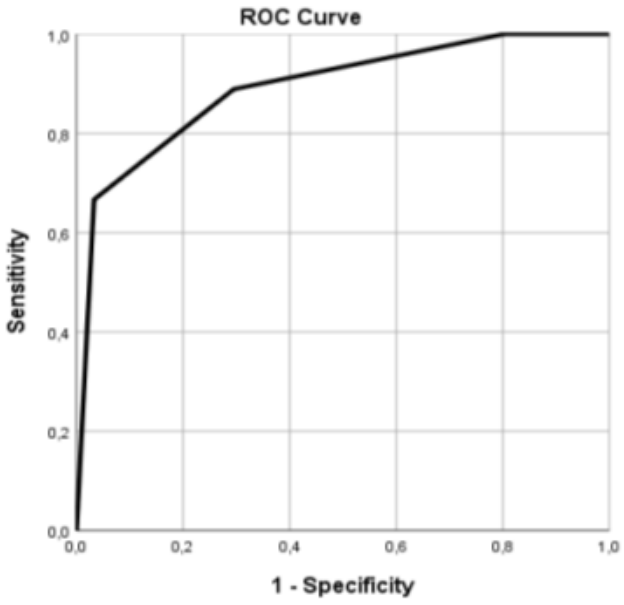
Figures

A.



B.

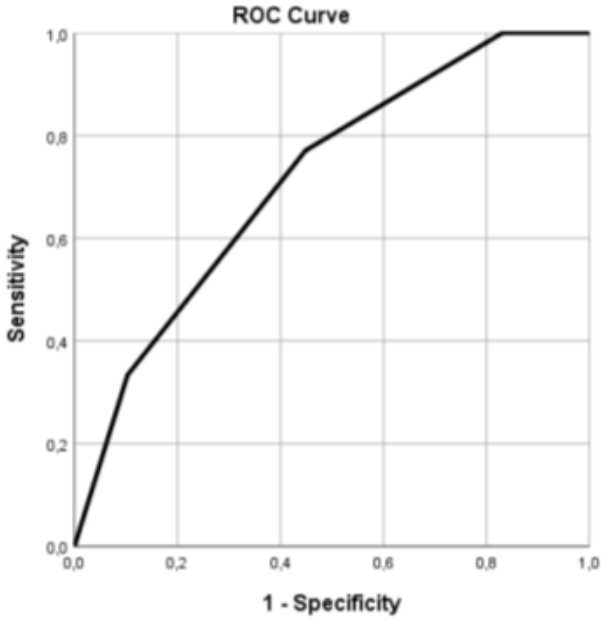


Figure 1

ROC curves of the derivation (A) and external sample (B) about the outcome “Exitus”

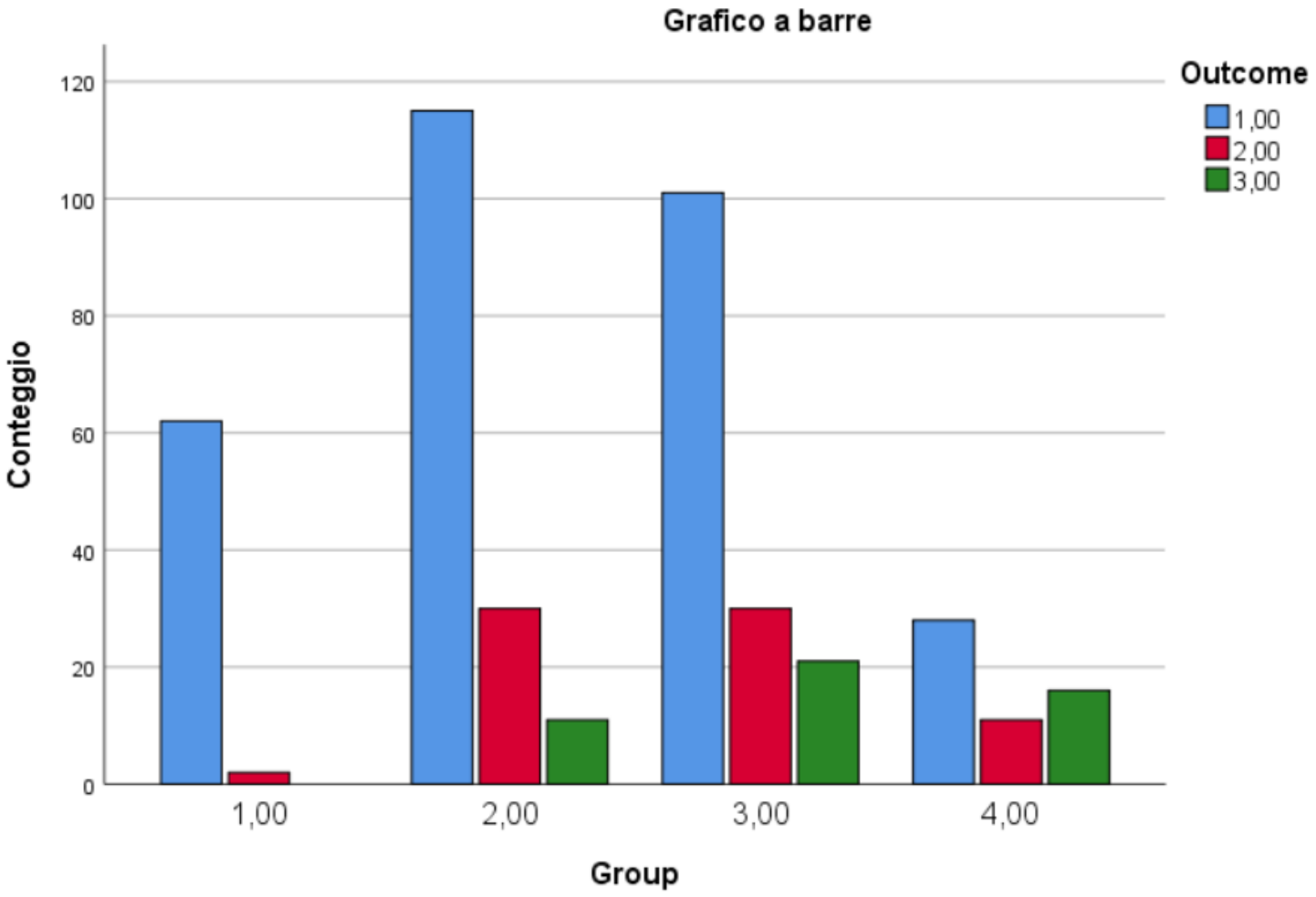


Figure 2

In the first Group are not dead people (outcome 3)