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Direct bilirubin and the neutrophil-to-monocyte ratio timely predict intensive care unit admission in patients with severe acute respiratory syndrome coronavirus-2 infection (COVID-19)

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Abstract

Objective: *Intensive care units (ICUs) collapsed under the global wave of coronavirus disease 2019 (COVID-19). Thus, we designed a clinical decision-making model that can help predict at hospital admission what patients with COVID-19 are at higher risk of requiring critical care.* **Methods:** *This was a cross-sectional study in 119 patients that met hospitalization criteria for COVID-19 including less than 30 breaths per minute, peripheral oxygen saturation < 93%, and/or ≥ 50% lung involvement on imaging. Depending on the need for critical care, patients were retrospectively assigned to ICU and non-ICU groups. Demographic, clinical, and laboratory parameters were collected at admission and analyzed by classification and regression tree (CRT).* **Results:** *Forty-five patients were admitted to ICU and 80% of them were men older than 57.13 ± 12.80 years on average. The leading comorbidity in ICU patients was hypertension. The CRT revealed that direct bilirubin (DB) > 0.315 mg/dl together with the neutrophil-to-monocyte ratio (NMR) > 15.90 predicted up to correctly in 92% of the patients the requirement of intensive care management, with sensitivity of 93.2%. Preexisting comorbidities did not influence on the tree growing.* **Conclusions:** *At hospital admission, DB and NMR can help identify nine in 10 patients with COVID-19 at higher risk of ICU admission.*

Keywords: *COVID-19. Severe acute respiratory syndrome coronavirus-2. Direct bilirubin. Neutrophil-to-monocyte ratio. Clinical decision-making model. Classification and regression trees.*

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that was first identified in Wuhan, China, and has rapidly spread to the rest of the world[1]. The vast majority of patients with COVID-19 experience a mild disease that self-limits in < 2 weeks, however, up to 15% of patients can develop severe forms of the disease including respiratory failure, multiple organ failure, and death[2]. Several studies have consistently reported that near 30% of patients with severe SARS-CoV-2 infection requires critical care, which alarmingly overwhelmed intensive care units (ICUs) during the first global wave of COVID-19 and is expected to happen now during the second wave of this infectious disease[3].

Quick admission to ICU clearly decreases mortality rates of patients seriously ill with COVID-19[4]. For this reason, there is a deep need for simple decision-making models that allow clinicians predicting from the very

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first moment of hospital admission what patients with severe SARS-CoV-2 infection might be ICU candidates. Recently, we demonstrated that risk factors such as the neutrophil-to-monocyte ratio (NMR) at admission can accurately predict in-hospital mortality in patients seriously ill with COVID-19 without having yet explored their utility in prioritizing ICU admission[5].

Classification and regression trees (CRTs) are predictive algorithms that provide decision-making models based on analyzing the influence of several independent numerical variables on a target variable[6]. Moreover, CRT can also model the potential influence of categorical variables on the main clinical outcome, which has recently popularized the use of these decision algorithms in clinical research[7,8]. In addition, CRT algorithms are able to predict a clinical outcome assuming that the relationship between dependent and independent variables occurs in a non-linear form, as previously reported for the development of complex human diseases[9]. Thus, we hypothesize that CRT might be a powerful tool in developing a clinical decision-making model that can help clinicians predict ICU admission in patients with severe SARS-CoV-2 infection. The purpose of this study was to analyze the most important demographic, clinical, and laboratory risk factors for designing a clinical decision-making model that can predict at hospital admission the need for critical care in patients with severe COVID-19.

Materials and Methods

Patients and study design

It was a cross-sectional, prospective, and analytical study in 119 individuals of both sexes, aged 18 years and older that met at least one of the following criteria of severe COVID-19: oxygen saturation levels (SpO_2) ≤ 93% on room air, respiratory distress ≥ 30 breaths per minute, and/or ≥ 50% lung involvement on imaging. Diagnosis of COVID-19 was confirmed by quantitative polymerase chain reaction following the World Health Organization technical guidance[10]. All eligible patients were originally admitted to the Emergency Department from October 5, 2020, to February 26, 2021, and depending on the clinical evolution were transferred to the ICU for ventilatory support. Patients were retrospectively grouped into two different clusters depending on the need for invasive mechanical ventilation in ICU according to the Clinical Care Guidelines for Influenza and SARS-CoV-2 of the Centers for Disease Control and Prevention[11]. Patients that met criteria of severe COVID-19 were enrolled in the study if they agreed to provide written informed consent previously approved by the Institutional Ethical Committee with registration number of the ethical code approval: DI/20/501/03/17. The study was conducted in rigorous adherence to the principles described in the 1964 Declaration of Helsinki and its posterior amendment in 2013. This study is reported in compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Patients were excluded from the study if they had previous diagnosis of chronic liver disease, endocrine disorders, and infectious diseases. Patients unable to provide written informed consent and pregnant or lactating women were also excluded from the study.

Demographic, clinical, and laboratory data

Demographic information, clinical data, and laboratory measurements were recorded at hospital admission. Demographic data included gender and age. Clinical data included previous diagnosis of obesity with body mass index ≥ 30 kg/m^2, Type 2 diabetes (T2D), high blood pressure ≥ 130/80 mmHg, chronic kidney disease (CKD), coronary heart disease (CHD), autoimmune disease, cancer, smoking, alcoholism, peripheral oxygen saturation, breath rate, heart rate, body temperature, odynophagia, chest pain, diarrhea, inpatient days, date of discharge or death, and drug therapy for COVID-19. Laboratory data were collected using the digital version of the electronic health record of the hospital and included blood glucose, lipid profile, liver function tests, kidney function tests, coagulation markers, hematic biometry, C-reactive protein, troponin I, ferritin, procalcitonin, myoglobin, and D-dimer. NMR resulted of dividing the total neutrophil count by the total monocyte count.

Statistics and CRT

Assessment of normality was performed using the Shapiro–Wilk test. Categorical variables were analyzed by the Chi-square test and are expressed as absolute values and percentages. Numerical variables were analyzed by the unpaired Student's t-test and are expressed as mean ± standard deviation. These statistical analyses were performed using the GraphPad Prism 6.01 software (GraphPad Software, La Jolla, CA 92037, USA) and differences were considered significant when $p < 0.05$. Numerical variables were used to build a CRT considering ICU admission as dependent variable. Then, the CRT was explored by categorical variables such as gender, obesity, T2D, hypertension,

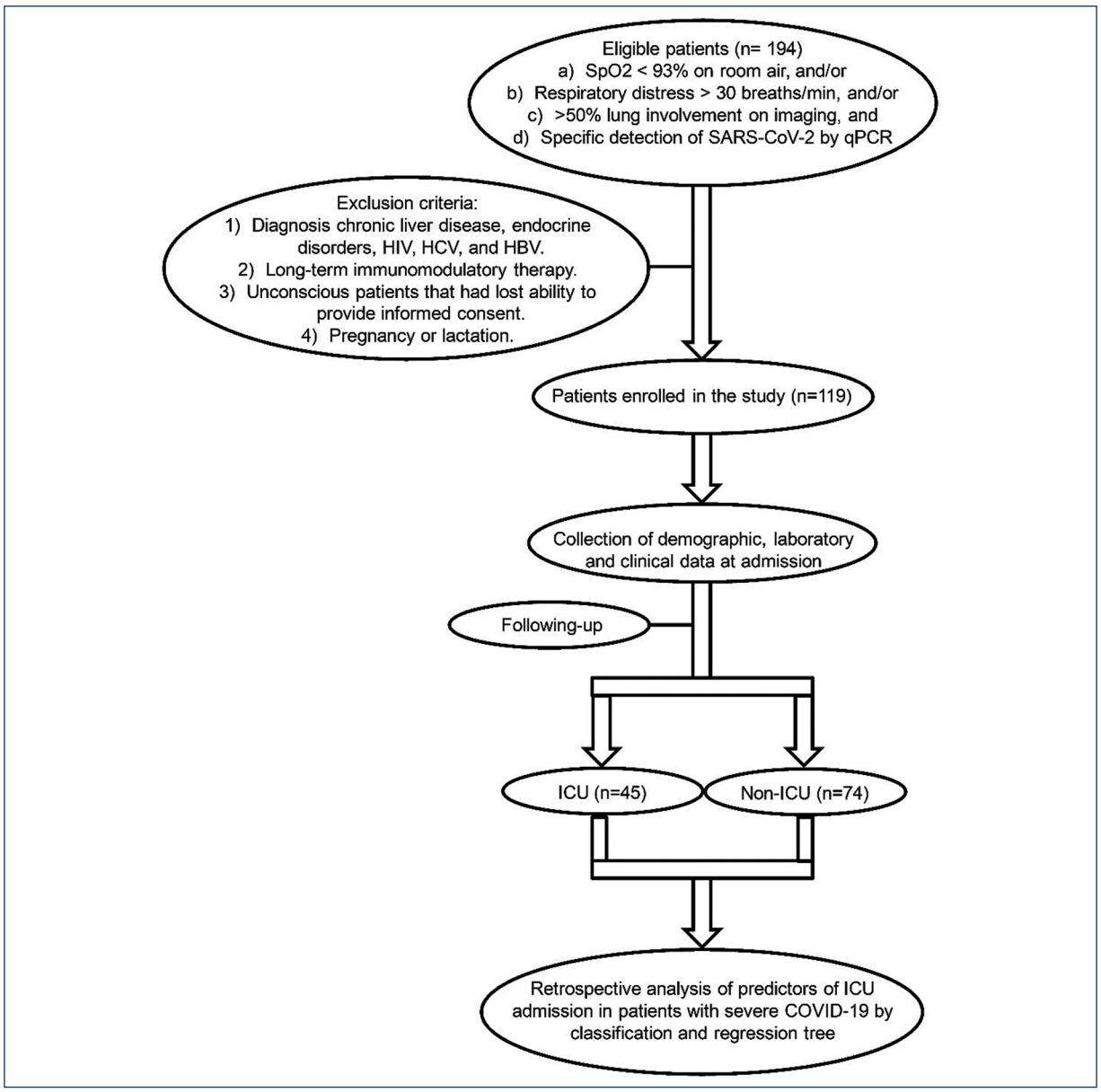

Figure 1. Schematic flowchart showing the selection process of patients enrolled in the study based on the inclusion and exclusion criteria. SpO_2: oxygen saturation level; SARS-CoV-2: novel severe acute respiratory syndrome coronavirus-2; qPCR: quantitative polymerase chain reaction; HIV: human immunodeficiency virus; HCV: hepatitis C virus; HBV: hepatitis B virus; COVID-19: coronavirus disease 2019.

CKD, and CHD that may influence the decision algorithm. The CRT was performed with the minimum number of cases in the parent node of 20% of the sample size, stopping rule for terminal nodes of 10%, 10-fold cross-validation, and tree pruning with a maximum acceptable difference in risk between the pruned tree and the sub-tree of 1 standard error. The CRT contained a root node, four terminal nodes, and three levels. Cutoff point, sensitivity, specificity, odds ratio (OR), and 95% confidence interval were calculated for each predicting variable of the CRT using the IBM SPSS Statistics Version 26.0 (IBM, Armonk, NY, USA).

Results

The selection process of patients enrolled in the study is shown in figure 1. After being admitted to the Department of Pneumology, 37.8% (n = 45) of patients with

Table 1. Demographic, clinical, and laboratory parameters in patients with severe COVID-19

Parameters	Total (n = 119)	Non-ICU (n = 74)	ICU (n = 45)	p-value
Gender (W/M)	33/86	24/50	9/36	0.142
Age (years)	54.46 ± 11.98	52.84 ± 11.24	57.13 ± 12.80	0.058
Obesity prevalence (%)	60 (50.4)	37 (50)	23 (51.1)	0.920
Comorbidities prevalence (%)	81 (68.1)	53 (71.6)	28 (62.2)	0.286
T2D prevalence (%)	62 (52.1)	40 (54.1)	22 (48.9)	0.584
Hypertension prevalence (%)	36 (30.3)	29 (39.2)	7 (15.6)	0.006*
Chronic kidney disease (%)	5 (4.2)	5 (6.8)	0 (0)	0.075
Coronary heart disease (%)	2 (1.7)	0 (0)	2 (4.4)	0.067
Autoimmune diseases (%)	3 (2.5)	1 (1.4)	2 (4.4)	0.297
Cancer (%)	1 (0.8)	1 (1.4)	0 (0)	0.434
Smoking (%)	27 (22.7)	17 (23.0)	10 (22.2)	0.807
Alcoholism (%)	16 (13.4)	10 (13.5)	6 (13.3)	0.978
Peripheral oxygen saturation (%)	82.61 ± 6.54	84.08 ± 5.62	80.18 ± 7.26	0.001*
Temperature (°C)	36.99 ± 0.562	37.01 ± 0.577	36.94 ± 0.539	0.513
Heart rate (breaths/min)	90.18 ± 12.24	88.30 ± 12.13	93.29 ± 11.91	0.030*
Breath rate (beats/min)	24.50 ± 3.72	23.95 ± 3.97	25.42 ± 3.11	0.035*
Dyspnea	106 (89.1)	64 (86.5)	42 (93.3)	0.246
Cough	102 (85.7)	62 (83.8)	40 (88.9)	0.440
Fever (≥37.3°C)	100 (84.0)	59 (79.7)	41 (91.1)	0.100
Myalgia	81 (68.1)	56 (75.7)	25 (55.6)	0.022*
Headache	48 (40.3)	31 (41.9)	17 (37.8)	0.657
Odynophagia	50 (42.0)	30 (40.5)	20 (44.4)	0.676
Chest pain	23 (19.5)	13 (17.6)	10 (22.7)	0.494
Diarrhea	34 (28.6)	23 (31.1)	11 (24.4)	0.437
Neutrophils ($\times10^3$/uL)	7.37 ± 3.25	6.87 ± 3.02	8.19 ± 3.47	0.030*
Lymphocytes ($\times10^3$/uL)	0.913 ± 0.425	0.992 ± 0.439	0.784 ± 0.371	0.009*
Monocytes ($\times10^3$/uL)	0.439 ± 0.231	0.467 ± 0.238	3922 ± 0.213	0.086
Neutrophil percentage (%)	81.86 ± 9.29	80.00 ± 9.73	84.93 ± 7.71	0.005*
Lymphocyte percentage (%)	12.27 ± 7.62	13.66 ± 8.25	9.99 ± 5.86	0.010*
Monocyte percentage (%)	5.56 ± 3.39	6.16 ± 3.65	4.57 ± 2.68	0.012*
Total bilirubin (mg/dL)	0.744 ± 0.461	0.641 ± 0.283	0.913 ± 0.625	0.002*
Direct bilirubin (mg/dL)	0.278 ± 0.285	0.212 ± 0.169	0.388 ± 0.388	0.001*
Indirect bilirubin (mg/dL)	0.465 ± 0.214	0.429 ± 0.164	0.525 ± 0.269	0.017*
AST (IU/L)	47.48 ± 30.59	42.87 ± 25.33	54.96 ± 36.69	0.037*
LDH (IU/L)	450.61 ± 185.87	417.43 ± 144.39	505.16 ± 230.59	0.012*
Prothrombin time (s)	11.82 ± 1.29	11.63 ± 1.04	12.12 ± 1.59	0.045*

(Continues)

Table 1. Demographic, clinical, and laboratory parameters in patients with severe COVID-19 *(Continued)*

Parameters	Total (n = 119)	Non-ICU (n = 74)	ICU (n = 45)	p-value
Base excess	– 3.18 ± 4.13	– 3.86 ± 3.63	– 2.07 ± 4.68	0.021*
NMR	23.77 ± 23.06	19.44 ± 14.13	30.88 ± 31.81	0.008*
Inpatient days	14.79 ± 9.23	12.66 ± 5.99	18.29 ± 12.22	0.001*
Mortality	43 (36.1)	12 (16.2)	31 (68.9)	0.000*
Drug regimen	Azithromycin, ceftriaxone, oseltamivir, enoxaparin sodium, dexamethasone, and acetaminophen			

Parameters were recorded at hospital admission. Laboratory parameters with significant differences are shown. Normality of data distribution was estimated by the Shapiro–Wilk test. The unpaired Student's t-test was used to compare numerical variables and data are presented as mean ± standard deviation. The Chi-squared test was used to compare categorical variables and data are expressed as absolute values and percentages.
*Differences were considered significant when $p < 0.05$.
W: women; M: men; T2D: type 2 diabetes; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; NMR: neutrophil-to-monocyte ratio.

severe COVID-19 needed being transferred to ICU (Table 1). Among patients admitted to ICU, 80% (n = 36) were men (Table 1). Patients that required critical care were, on average, 5 years older and showed lower hypertension prevalence than patients treated in non-ICU facilities (Table 1). There were no significant differences between non-ICU and ICU patients with respect to dyspnea, cough, headache, chest pain, diarrhea, peripheral oxygen saturation, and body temperature (Table 1). In contrast, heart rate significantly increased in ICU patients as compared to non-ICU patients (Table 1). Function liver tests including conjugated and unconjugated bilirubin and AST were significantly higher in ICU patients than non-ICU patients. Similarly, there were significant differences between non-ICU and ICU patients with respect to LDH, prothrombin time, and cell counts of lymphocytes, monocytes, and neutrophils (Table 1). Notably, NMR was 1.5-fold increase in ICU patients as compared to non-ICU patients (Table 1). Hospitalization days were longer in patients admitted to ICU, who also showed higher in-hospital mortality than patients treated in non-ICU facilities. There were no significant differences between non-ICU and ICU patients with respect to the six-drug regimen used to treat them that included azithromycin, ceftriaxone, oseltamivir, enoxaparin sodium, dexamethasone, and acetaminophen (Table 1).

The CRT decision algorithm for prioritizing ICU admission of patients with severe COVID-19 is shown in figure 2. The root node contains the total of 119 patients, where 37.8% (n = 45) required being admitted to the ICU. From the analysis of 59 parameters used to build the CRT, the value of direct bilirubin (DB) at hospital admission was the most important risk factor to allocate patients with severe COVID-19 to the ICU. In fact, the node 1 shows that DB with cutoff point > 0.315 mg/dl can initially help to triage up to 46% (n = 21) of patients with COVID-19 to the ICU with sensitivity of 46.7%, specificity of 89.2%, and OR of 7.219 (95% CI, 2.823-18.458) (Fig. 2). The node 2 indicates that patients who apparently did not meet ICU admission criteria by having DB ≤ 0.315 mg/dl can be additionally explored using the value of NMR with cutoff point > 15.90 at hospital admission (Fig. 2). The node 3 shows that NMR > 15.90 can be used as a complementary risk factor to triage another 46% (n = 21) of patients from the total population at risk of requiring ventilatory support (Fig. 2). In this way, the node 4 shows that values of DB and NMR at hospital admission allow predicting up to 92% (n = 116) of patients with severe COVID-19 that might require critical care, with sensitivity of 93.2%, specificity of 26.7%, and OR of 5.018 (95% CI, 1.633-15.422) (Fig. 2). Neither gender nor comorbidities such as obesity, T2D, hypertension, CKD, and CHD had an influence on the tree growing (data not shown).

Discussion

The first global wave of COVID-19 reached a peak in the months of March, April, May, and June of this year with thousands of patients admitted to critical care units across Europe, America, and the rest of the world[12-15]. Nowadays, the entire world is experiencing a second wave of COVID-19 that once again is alarmingly overwhelming ICUs[16-18]. For this reason, there is a strong sense of urgency to develop simple clinical models that allow predicting what patients with severe COVID-19 are at higher risk of requiring critical care with the aim of increasing patient's survival and optimizing ICU resources.

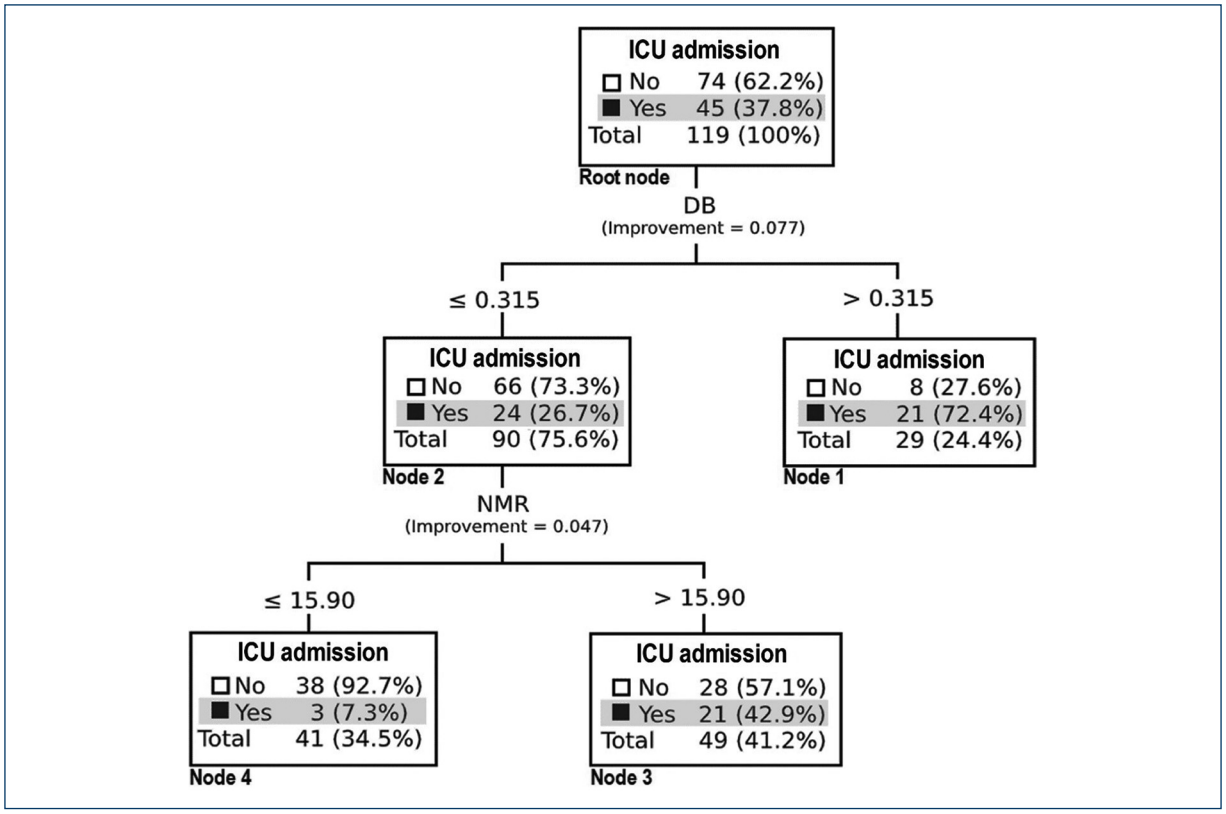

Figure 2. CRT decision algorithm for predicting ICU admission in patients with severe COVID-19. The root node contains the total of 119 patients, where 37.8% (n = 45) required being admitted to the ICU. The node 1 shows that DB with cutoff point > 0.315 mg/dl can initially help to triage up to 46% (n = 21) of patients with COVID-19 to the ICU. The node 2 indicates that patients who apparently did not meet ICU admission criteria by having DB ≤ 0.315 mg/dl can be additionally explored using the value of NMR with cutoff point > 15.90 at hospital admission. The node 3 shows that NMR > 15.90 can be used as a complementary risk factor to triage another 46% (n = 21) of patients from the total population at risk of requiring ICU admission. The node 4 shows that values of DB and NMR at hospital admission allow predicting up to 92% (n = 116) of patients with severe COVID-19 that might require critical care with high sensitivity. Neither gender nor comorbidities such as obesity, T2D, hypertension, CKD, and CHD had an influence on the tree growing. The CRT was performed with the minimum number of cases in the parent node of 20% of the sample size, stopping rule for terminal nodes of 10%, 10-fold cross-validation, and tree pruning with a maximum acceptable difference in risk between the pruned tree and the sub-tree of 1 standard error, using the IBM SPSS Statistics Version 26.0 (IBM, Armonk, NY, USA). NMR resulted of dividing the neutrophil count by the monocyte count.
ICU: intensive care unit; DB: direct bilirubin; NMR: neutrophil-to-monocyte ratio.

Here, we propose a clinical decision-making model based on the values of DB and NMR at admission that allows predicting up to 92% of the total patient population with severe COVID-19 that might need ICU admission (Fig. 3). Bilirubin is a waste product of hemoglobin catabolism whose water-soluble fraction is secreted into the bile in the form of conjugated bilirubin or DB. Serum levels of DB have been shown to elevate in patients with HBV or HCV and associate with increased liver inflammation and fibrosis[19,20]. In addition, DB serum values can increase as a result of systemic infection in patients with sepsis-induced cholestasis[21]. This previous information demonstrates that DB is a biochemical marker that elevates by hepatotropic viral infections and sepsis, both conditions highly frequent in critical patients with the most severe forms of COVID-19[22,23]. In this study, DB serum levels significantly increased in critical patients with SARS-CoV-2 infection. In parallel, the clinical decision algorithm revealed that DB was the most important risk factor for considering admission of patients with severe COVID-19 to ICU. Cholangiocytes have been shown to highly express the angiotensin-converting enzyme 2 receptor that acts as the SARS-CoV-2 entry point through Spike protein S1 that, in turn, leads to DB accumulation and liver dysfunction in these patients[24,25]. Considering all

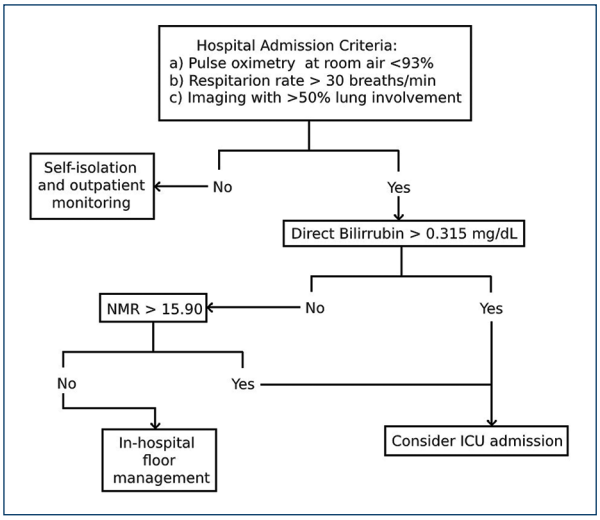

Figure 3. Clinical decision-making model based on the values of DB and NMR at admission for predicting ICU admission in patients with severe COVID-19. At hospital admission, the levels of direct bilirubin and NMR should be measured in patients with severe COVID-19 confirmed by qPCR that also shows pulse oximetry at room air < 93%, respiratory rate > 30 breaths per minute, and/or ≥ 50% lung involvement on imaging. If direct bilirubin > 0.315 mg/dL or NMR ≥ 15.90, the patient should be considered for being admitted to the intensive care unit. NMR resulted of dividing the neutrophil count by the monocyte count.
NMR: neutrophil-to-monocyte ratio.

the above information, it is feasible to assume that BD plays a pivotal role in worsening the severity of COVID-19 and can be used as marker of critical condition in this viral infection. However, we cannot dismiss that some patients with critical SARS-CoV-2 infection might also have an undiagnosed liver condition that, in turn, may increase DB levels and aggravate COVID-19. For this reason, we propose that patients seriously ill with COVID-19 should be fully explored in terms of any hepatic disorder that may increase DB levels and decrease patient's survival probability.

As we previously reported, NMR accurately predicts in-hospital mortality in patients with severe SARS-CoV-2 infection[5]. Now, our clinical decision-making model indicates that NMR with a different cutoff value can be used to complement identification of patients seriously ill with COVID-19 at risk of requiring critical care. Neutrophils play a pivotal role in defending epithelial cells of the lung against the SARS-CoV-2 invasion by secreting pro-inflammatory cytokines and orchestrating immune cell recruiting through chemokine production[26]. However, neutrophils also appear to be a double-edged sword in COVID-19-related pneumonia by mediating a pro-inflammatory cytokine storm that intensifies both neutrophilia and lesions in the lungs of patients infected with SARS-CoV-2[27]. On the other side, monocytes are white blood cells that can be sorted in three different subpopulations according to the cell surface expression of the cluster of differentiation (CD) 14 and CD16. In this way, circulating monocytes expressing high CD14 levels without showing CD16 expression are identified as classical monocytes and comprise the largest monocyte subset in humans (~75-80%)[28]. In parallel, monocytes that express CD14 and CD16 are called intermediate monocytes, while monocytes that show CD16 expression with low CD14 production are referred to as non-classical monocytes[28]. Classical monocytes are not only the largest monocyte subpopulation in blood but also the main monocytic source of interleukin (IL-) 10, a cytokine with potent anti-inflammatory actions[29,30]. Besides playing anti-inflammatory functions by producing IL-10, classical monocytes also exert important roles in wound healing and tissue repair[31]. Altogether, these are the main reasons behind the idea that monocytopenia is associated with the most severe forms of COVID-19[32]. Thus, increased neutrophilia and monocytopenia reflect the marked imbalance between pro-inflammatory and anti-inflammatory immune responses in patients critically ill with COVID-19[33]. Concurring with this idea, our clinical decision algorithm indicates that in patients with severe COVID-19, the ratio between neutrophils and monocytes is a better predictor of ICU needing than the cell count of neutrophils or monocytes separately.

Clinical decision-making models are a useful tool to predict important clinical outcomes based on studying the relationship between dependent and independent variables that behave in a non-linear form as occurs in disease onset and progression[34]. Here, we offer a clinical decision-making model based on CRT analysis that allows predicting what patients with severe SARS-CoV-2 infection will require ICU admission, as early as they arrive to the hospital. In this sense, Izquierdo et al. recently reported in a large cohort study that age > 40 years, fever > 39°C, tachypnea, and respiratory crackles are accurate predictors of ICU admission in patients with COVID-19[35]. However, it has been reported that only 43.8% of patients with COVID-19 present fever at hospital admission, whereas 88.7% can develop increased body temperature after several days of hospitalization[36]. Similarly, tachypnea and dyspnea can appear in a few percent of patients with COVID-19, which may also lead to underestimate the real number of patients at risk of requiring ICU admission in the

upcoming days[37]. To this respect, our study shows that DB and NMR can predict ICU needing at hospital admission without necessarily waiting a long time to see disease worsening, a notion that might help optimizing ICU resources with the aim of reducing mortality risk. Another work conducted in a large cohort study reported that the National Early Warning Score can predict ICU admission with sensitivity of 71.4%[38]. In this regard, our clinical decision-making model is able to predict ICU admission of patients with severe COVID-19 with sensitivity of 93.2%, thus increasing the chance of accurately identifying patients at risk of requiring critical care. Although our model presents low specificity, other relevant tools have been historically used with low specificity and high sensitivity, as the Glasgow-Blatchford scale for survival and need for intervention predictions in upper gastrointestinal bleeding, permitting hospital resources administration[39]. In the same way, in COVID-19 context, chest computed tomography has presented low specificity but a very high sensitivity for diagnosis, allowing to accurately identify infected patients with typical symptoms who had a negative RT-PCR result[40]. Moreover, a recent study proposes the use of the ABC-GOALS score that consists of different variables such as arterial pressure, obesity, glucose, and X-ray image, among others, to predict ICU admission in patients with severe COVID-19[41]. Besides this study reports sensitivity values below 90%, we consider that clinical models of critical care triage should be as simple and fast as possible with the aim of timely improving ICU admission of patients with severe SARS-CoV-2 infection. In this sense, DB and NMR can be quickly measured at hospital admission with the intention of timely predicting what patients are at risk of requiring critical care soon. In addition, we encourage the testing of other molecules or methods at admission to predict ICU needing to augment specificity and preserve high sensitivity.

The sample size was a limitation of this study. Despite having enrolled more than 100 patients with severe SARS-CoV-2 infection (n = 119), the number of patients requiring ICU admission was, in some sense, small (n = 45). A larger sample size may help strengthen our observations with the aim of increasing their accuracy in a clinical scenario.

Conclusions

This study proposes for the 1st time a clinical decision-making model where DB with cutoff point > 0.315 mg/dl and NMR with cutoff point > 15.90 at admission can quickly predict the need for critical care in patients seriously ill with COVID-19 (Fig. 3). This clinical decision-making model based on CRT analysis allows predicting in an easy manner what patients with severe COVID-19 are at risk of requiring critical care with sensitivity of 93.2%. The search for clinical models to timely predict ICU admission is of great importance during the second global wave of COVID-19 and might allow optimizing ICU resources and decreasing in-hospital mortality rates.

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Conflicts of interest

The authors declare that do not exist conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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