

DEVELOPMENT OF SIMPLE AND SENSITIVE SCORE TO ASSESS THE RISK OF PNEUMONIA IN COVID-19 PATIENTS

MACARENA HORMANSTORFER^{1*}, MARTIN A. RAGUSA¹, LUCIA POGGIO¹, JORGE MOREIRA-FACUNDO¹, ZULMA ORELLANA-VILLA¹, FLORENCIA A. BOBROWSKI¹, JOAQUIN MARTINEZ-SERVENTI¹, SANTIAGO N. PIOMBI ADANZA¹, JOSE A. ENRIQUE BARLETTA², ALICIA SISTO², HUGO DELLE-PIANE¹, JUAN M. CARRILLO¹, JOSE L. PRESAS¹, AND FRANCISCO PAULIN¹

Divisions of ¹Internal Medicine and ²Infectious Diseases, Hospital Juan A. Fernández, Buenos Aires, Argentina

ABSTRACT

Background: Severe pneumonia is the most common cause of intensive care unit (ICU) admission and death due to novel coronavirus (SARS-CoV-2) respiratory disease (COVID-19). Due to its rapid outbreak, units for the evaluation of febrile patients in the pre-hospital setting were created. **Objective:** The objective of the study was to develop a sensitive and simple tool to assess the risk of pneumonia in COVID-19 patients and thus select which patients would require a chest imaging study. **Materials and Methods:** We conducted a cross-sectional study in a cohort of individuals with suspected COVID-19 evaluated in a public academic healthcare center in Buenos Aires city. All adult patients with positive RT-PCR assay for SARS-CoV2 between April 24 and May 19 of 2020 were included in the study. Pneumonia was defined as the presence of compatible signs and symptoms with imaging confirmation. Univariate and multivariate logistic regression was performed. A risk indicator score was developed. **Results:** One hundred and forty-eight patients were included, 71 (48%) received the diagnosis of pneumonia. The final clinical model included four variables: age ≥ 40 years, cough, absence of sore throat, and respiratory rate ≥ 22 . To create the score, we assigned values to the variables according to their ORs: 2 points for respiratory rate ≥ 22 and 1 point to the other variables. The AUC of the ROC curve was 0.80 (CI 95% 0.73-0.86). A cutoff value of 2 showed a sensitivity of 95.7% and a specificity of 43.24%. **Conclusion:** This sensible score may improve the risk stratification of COVID-19 patients in the pre-hospital setting. (REV INVEST CLIN. 2021;73(1):52-8)

Key words: COVID-19. SARS-CoV-2. Pneumonia. Risk indicator score.

INTRODUCTION

In December 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China. Rapidly, in

January 2020, Chinese scientists sequenced the genome of the novel coronavirus designated SARS-CoV2¹. This agent has been found to be responsible for several cases of severe acute respiratory syndrome around the world. The coronavirus disease (COVID-19)

*Corresponding author:
Macarena Hormanstorfer
E-mail: hormanstorferm@gmail.com

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was declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and was defined as pandemic on March 11, 2020. At the end of July, the WHO reported around 17.106.007 cases of COVID-19 and 668.910 deaths². Despite public health efforts aimed to control the disease, numerous health-care systems have collapsed because of COVID-19^{3,4}. On March 3, 2020, the first case was confirmed in Argentina. Almost 3 months later, the total number of COVID-19 cases is 191.302. Most of them reside in Buenos Aires⁵.

Argentina is a developing country where a significant proportion of the population receives medical attention in the public health-care system. Due to the rapid spread of this infectious disease, and the imminent collapse of public health-care system, health and government authorities implemented measures to slow the spread of the disease and guarantee medical assistance to suspected cases. Twenty Febrile patients' units (FPU) were created to expand patient care capacity. There, suspected cases are identified, and the tests are performed. As these units are close to hospitals, they also make triage admission and define which patients require emergency department evaluation, according to their severity. The Fernandez Hospital is an academic public healthcare center located in Buenos Aires city, designated to give attention to suspected and confirmed cases of COVID-19.

Epidemiological and clinical characteristics of patients with COVID-19 have been reported in several international studies, most of them from China. Those studies described the spectrum of disease severity, which includes an asymptomatic course, or mildly symptomatic upper respiratory tract illness, to severe viral pneumonia with radiological opacities, respiratory failure, and death⁶. Approximately 15% of the infected patients will develop severe disease and require hospitalization, and 5% will require admission to an intensive care unit⁷. The most common reported reason for requiring intensive care admission has been the need of respiratory support⁶. Patients who require ICU admission tend to be older and have a higher prevalence of comorbid conditions such as hypertension and diabetes, among others^{6,8,9}. Regarding radiological findings, patients with COVID-19 showing lung opacities compatible with pneumonia may have a worse prognosis than those without them¹⁰. That group of patients may double the odds of progression

to severe disease, compared with patients with normal chest image¹¹⁻¹⁴.

Clinical prediction rules are a useful resource to know which patients are at risk of having a specific outcome. The knowledge of isolated risk factors is often not sufficient to determine the probability of having a specific event. To the best of our knowledge, rules to assess the risk of pneumonia in COVID-19 patients are lacking. A simple and sensible clinical rule to assess the risk of pneumonia composed by clinical and demographic features collected at the patient first assessment could be a useful tool in the pre-hospital setting to rule out the diagnosis of pneumonia without the realization of a chest image. The aim of this observational cross-sectional study was to develop that rule.

MATERIALS AND METHODS

We conducted a cross-sectional study based on the analysis of a prospective cohort of individuals with suspected COVID-19 admitted to a general ward after being initially evaluated at febrile patients' units (FPU) and emergency department (ED) of Fernandez Hospital, in Buenos Aires city. All patients who met the definition of suspected case were tested. If the first test was negative and the patient had compatible signs, symptoms, or chest images findings, a second test was performed. Patients with the diagnosis of other acute respiratory disease were excluded from the study. All adult patients with positive RT-PCR assay for SARS-CoV-2 in nasal or pharyngeal swab evaluated between April 24 and May 19 of 2020 were included in the study. The following data were consigned in a structured form during the patient's first evaluation: epidemiological and demographic data, comorbidities (diabetes, obesity, HIV infection, chronic kidney disease, alcohol abuse, COPD, asthma, smoking history, tuberculosis infection, hypertension, congestive heart failure, and coronary disease), use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), new signs and symptoms at disease onset, vital signs at the ED or the FPU (blood pressure, temperature, heart rate, respiratory rate, and oxygen saturation), modified NEWS score, qSOFA and CURB 65 scores, blood tests, and chest images. A member of the data management team and review by a second member of that

team charged data submitted by physicians on paper forms in a digital database. Clinical manifestations related to chronic conditions (i.e., COPD) were not considered. The diagnosis of pneumonia was defined as the presence of compatible signs and symptoms (fever with cough or difficult breathing) with imaging confirmation. All patient included has at least one of the following chest images to make a pneumonia diagnosis: chest X-ray (usually made at ED), lung ultrasound (usually made at FPU), or chest CT (performed in patients in whom the diagnosis of pneumonia was still not clear after the realization of X-ray or lung ultrasound).

Statistical analysis

Comparisons between groups were made using a t-test, Mann–Whitney test, and Chi-square. Univariate logistic regression was performed, with the presence of pneumonia as a dependent variable. Continuous variables were categorized according to cutoff points defined by receiver operating curve analysis. Statistical significance was analyzed with Wald test. Variables with a $p < 0.1$ were considered candidates for the multivariate analysis. The decision to include a variable in the definitive model was guided with the likelihood ratio test. We prioritized those variables which can be easily measured without medical equipment. Clinical significance was defined with a $p < 0.05$. The Hosmer–Lemeshow goodness of fit test was used to evaluate the model calibration. A risk indicator score was developed and values were assigned to the included variables according to regression coefficients and their corresponding odd ratios. The discrimination accuracy of the score was expressed as the area under the receiver operating curve. Regarding the sample size, minimum of 50 cases had to be included to have enough power to build a score with five risk factors, according to the “one variable per ten events” rule¹⁵. We performed an internal validation of the model with the Bootstrap method. The manuscript was written according to the STROBE initiative for the communication of observational studies¹⁶. The Institutional Ethics Committee of our hospital reviewed and approved the study.

RESULTS

Between April 24 and May 19 of 2020, 348 patients with suspected COVID-19 were admitted in the

Fernandez Hospital, derived from the ED or the FPU. Of them, 200 had a negative test for SARS-CoV-2 and were excluded from the study. Baseline characteristics of patients with a positive test for SARS-CoV-2 ($n = 148$) are presented in Table 1. The mean (SD) age was 42.7 years (16.5), with a predominance of male gender (56.7%). The most common symptoms at baseline were fever (66.9%), headache (56%), and cough (62%). A total of 71 patients (48%) received the diagnosis of pneumonia.

The comparison between groups according to the presence or absence of pneumonia is shown in Table 1. Patients with pneumonia were older and more likely to present fever, cough, dyspnea, and thoracic pain. Those patients without pneumonia were more likely to have a sore throat. Patients with pneumonia had a higher temperature, respiratory rate and NEWS score, and lower oxygen saturation. Regarding laboratory findings, lymphopenia, elevated C reactive protein, and lactate dehydrogenase were more frequent in pneumonia patients. We found no difference between groups in gender, comorbidities, qSOFA, and CURB-65 scores.

Regarding the lung images of patients with pneumonia, 34 patients (47%) were diagnosed with X-ray and 24 (33%) with lung ultrasound. In 31 cases (43%), the diagnosis of pneumonia was achieved or confirmed with a CT scan.

We studied the association between demographic and baseline clinical characteristics and the presence of pneumonia. Eight variables were associated with the diagnosis of pneumonia in univariate analysis (Table 2): age ≥ 40 years, presence of cough, absence of sore throat, respiratory rate ≥ 22 , temperature $\geq 37.5^\circ\text{C}$, oxygen saturation $\leq 94\%$, dyspnea, and male gender. All these variables were included in the initial multivariate analysis. The first model (not shown) was modified according to its statistical performance and clinical applicability.

The final clinical model included four variables: age ≥ 40 years, cough, absence of sore throat, and respiratory rate ≥ 22 (Table 3). To develop the risk indicator score, we assigned values to the included variables according to their regression coefficients and the corresponding odd ratios. The analysis of the discriminatory capacity of the rule showed an AUC of 0.80 (CI 95% 0.73–0.86) (Fig. 1). We chose a value of 2 points

Table 1. General characteristics of patients with confirmed COVID-19 infection admitted in Fernández Hospital between April 24 and May 19 of 2020. Comparison between patients with and without pneumonia

	Total (n=148)	Patients with pneumonia (n=71)	Patients without pneumonia (n=77)	p value
Demographics				
Age, mean (SD)	42.71 (16.51)	47.73 (14.7)	38.22 (16.83)	<0.001
Male gender, n (%)	84 (56.7)	46 (64.79)	38 (49.35)	0.058
Comorbidities				
Obesity, n (%)	25 (16.89)	15 (21.13)	10 (12.99)	0.187
Pregnant, n (%)	2 (1.35)	1 (1.3)	1 (1.41)	0.954
HIV infection, n (%)	4 (2.7)	2 (2.82)	2 (2.6)	0.934
Chronic kidney disease, n (%)	1 (0.68)	0 (0)	1 (1.3)	0.335
Current smoker, n (%)	13 (8.78)	7 (9.09)	6 (8.45)	0.891
Alcohol abuse, n (%)	7 (4.73)	1 (1.41)	6 (7.79)	0.068
COPD, n (%)	1 (0.68)	1 (1.41)	0 (0)	0.296
Asthma, n (%)	8 (5.41)	2 (2.82)	6 (7.79)	0.181
History of TBC infection, n (%)	6 (4.05)	2 (2.82)	4 (5.19)	0.464
Hypertension, n (%)	21 (14.19)	13 (18.31)	8 (10.39)	0.168
Congestive heart failure, n (%)	2 (1.35)	1 (1.41)	1 (1.3)	0.954
Coronary disease, n (%)	2 (1.35)	0 (0)	2 (2.6)	0.172
ACEIs, n (%)	8 (5.44)	6 (8.57)	2 (2.6)	0.111
ARBs, n (%)	4 (2.72)	3 (4.24)	1 (1.3)	0.266
Symptoms				
Fever, n (%)	97 (66.9)	54 (76.06)	43 (58.11)	0.022
Dyspnea, n (%)	43 (29.86)	29 (41.43)	14 (18.92)	0.003
Cough, n (%)	90 (62.07)	51 (71.83)	39 (52.7)	0.018
Sore throat, n (%)	46 (31.72)	13 (18.57)	33 (44)	0.001
Vomits, n (%)	12 (8.33)	7 (10)	5 (6.76)	0.482
Diarrhea, n (%)	26 (18.06)	15 (21.43)	11 (14.86)	0.306
Myalgias, n (%)	49 (33.79)	25 (35.21)	24 (32.43)	0.724
Arthralgias, n (%)	20 (13.89)	13 (18.57)	7 (9.56)	0.114
Malaise, n (%)	66 (45.21)	36 (50.7)	30 (40)	0.194
Headache, n (%)	82 (56.16)	38 (54.29)	44 (57.89)	0.661
Conjunctival injection, n (%)	9 (6.29)	2 (2.9)	7 (9.46)	0.106
Chest pain, n (%)	16 (11.11)	12 (17.14)	4 (5.41)	0.025
Confusion, n (%)	1 (0.69)	1 (1.43)	0 (0)	0.302
Physical examination				
Systolic blood pressure, mean (SD)	121.63 (15.37)	121.88 (14.28)	121.4 (16.46)	0.854
Temperature, mean (SD)	36.89 (0.97)	37.09 (0.97)	36.7 (0.94)	0.019
Heart rate, mean (SD)	92.88 (14.98)	94.95 (16.02)	90.87 (13.71)	0.107
Respiratory rate, mean (SD)	19.85 (3.9)	21.34 (4.29)	18.43 (3.09)	<0.001
Oxygen saturation, mean (SD)	96.15 (2.25)	95.18 (2.5)	97.11 (1.46)	<0.001

(Continues)

Table 1. General characteristics of patients with confirmed COVID-19 infection admitted in Fernández Hospital between April 24 and May 19 of 2020. Comparison between patients with and without pneumonia (*continued*)

	Total (n=148)	Patients with pneumonia (n=71)	Patients without pneumonia (n=77)	p value
Physical examination				
NEWS score at admission, median (IQR)	2 (1-4)	3 (2-5)	1 (0-3)	<0.001
CURB 65 at admission, median (IQR)	1 (0-1)	1 (0-1)	1 (0-1)	0.71
qSOFA at admission, median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0.221
Blood tests				
Platelets, mean (SD)	213.4 (105.4)	215.41 (80.95)	211.51 (124.78)	0.827
Lymphocytes%, mean (SD)	23.91 (11.56)	20.66 (9.61)	26.97 (12.45)	0.001
RCP, median (IQR)	2.4 (0.7-4.84)	4.48 (2.93-7.2)	1 (0.5-2.2)	<0.001
LDH, median (IQR)	239.5 (200-304)	272 (218-380)	211 (198-280)	<0.001

COPD: chronic obstructive pulmonary disease; TBC: tuberculosis disease; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; RCP: reactive protein C; LDH: lactate dehydrogenase.

Table 2. Univariate and multivariate logistic regression analysis with the presence of pneumonia as dependent variable. The adjusted ORs are shown only in variables included in the final model

	Unadjusted OR	CI 95%	Adjusted OR	CI 95%
Age \geq 40 years	4.72	2.35-9.48	3.49	1.59-7.68
Cough	2.28	1.14-4.56	3.21	1.37-7.5
Absence of sore throat	3.44	1.61-7.33	3.15	1.26-7.86
Respiratory rate \geq 22	4.52	2.12-9.63	5.93	2.38-14.76
Temperature \geq 37.5	3.01	1.49-6.08	—	—
Dyspnea	3.03	1.42-6.42	—	—
Male gender	1.88	0.97-3.65	—	—
Oxygen saturation \leq 94%	19.14	4.32-84.78	—	—

Table 3. Variables included in the risk indicator score

Variable	Points
Age \geq 40	1
Cough	1
Absence of sore throat	1
Respiratory rate \geq 22 pm	2

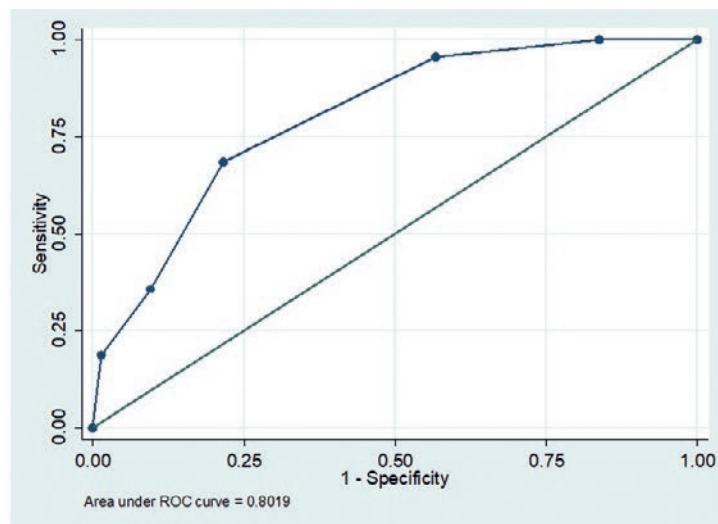
as the best cutoff of the rule, with a sensitivity of 95.7% and a specificity of 43.24%. We prioritized sensitivity over specificity because the score was conceived as a potential tool to rule out the diagnosis of pneumonia without the realization of a chest image in a pre-hospital setting.

The calibration accuracy of the final model showed good results (Hosmer–Lemeshow goodness of fit test $p = 0.59$). The internal validation with Bootstrap method demonstrated that after 1000 replications, the score showed an AUC of 0.80 (CI 95% 0.73-0.86; $p < 0.001$).

DISCUSSION

This study shows that certain clinical and demographic factors (such as age \geq 40 years, cough, absence of sore throat, respiratory rate \geq 22, temperature \geq 37.5, oxygen saturation \leq 94%, dyspnea, and male gender) are associated with the presence of pneumonia in patients with COVID-19. We created

Figure 1. Receiver operating characteristic curve of the risk indicator score developed to predict the presence of pneumonia in COVID 19 patients. It shows an AUC of 0.80 (CI 95% 0.73-0.86). A cutoff value of 2 points has a sensitivity of 95.7% and a specificity of 43.24%.



a score to assess the risk of pneumonia in COVID-19 patients based on 4 of these risk factors that showed a good discriminatory capacity. To the best of our knowledge, this is the first risk indicator score developed to identify pneumonia in COVID-19 patients.

Risk factors associated with worse prognostic in patients with COVID-19 pneumonia have been described in several international studies^{17,18}. Fei et al. showed in a retrospective multicentric cohort study of 191 patients with COVID-19 pneumonia, that older age (OR 1.10 95% CI 1.03-1.17 per year increase; $p = 0.0043$) higher SOFA score (OR 5.65, 95% CI 2.61-12.23; $p < 0.0001$), and d-dimer greater than 1 $\mu\text{g/mL}$ (OR 18.42, 95% CI 2.64-128.55; $p = 0.0033$) on admission were associated with an increased risk of death during hospitalization⁸. Chamin et al. reported in a retrospective cohort study of 201 patients with COVID-19 pneumonia that risk factors associated with the development of acute respiratory distress syndrome (ARDS) or death were older age (HR 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ dysfunction (higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44-1.79 and HR, 1.30; 95% CI,

1.11-1.52, respectively] and D-dimer elevation [HR, 1.03; 95% CI, 1.01-1.04 and HR, 1.02; 95% CI, 1.01-1.04, respectively])⁹. In addition to these findings, radiological abnormalities in patients with COVID-19 infection have also shown an association with worse prognosis^{10,19-22}. A group of authors found that some specific chest CT patterns (such as consolidation or crazy-paving sign) were related to severe disease. Another group of researchers utilized a CT score to calculate the extension of lung opacities and found that patients with higher values of the score had worse prognosis²⁰. All this information shows the ability of chest images to detect patients at risk of presenting a severe course of the disease and highlights the relevance of the diagnosis of pneumonia in patients with suspected COVID-19. However, performing a chest image is not easy because the resource is not always available in the pre-hospital setting. A simple score to safely rule out pneumonia in COVID-19 patients could help to reduce the number of suspected cases that need imaging. This may improve the risk stratification in the pre-hospital setting, leaving hospital resources free for patients with a worse prognosis. In summary, we believe that the ability of this score to rule out the presence of lung opacities in the chest images makes it a useful tool in the management of COVID-19 patients.

Our study has limitations. First, we developed the score with information from admitted patients, but it was conceived to be utilized in a different clinical scenario (the pre-hospital evaluation). This difference may introduce a context bias²³. Second, the diagnosis of pneumonia was achieved with different methods, depending on the place where the patient was initially evaluated (FPU or ED). In addition, the physicians registering forms with clinical data were not blinded to imaging results. This fact could imply the presence of test review bias. On the other side, the radiologist that interpreted the images may have been aware of clinical data, which could introduce diagnostic review bias²³. We believe that, although it has limitations, our study has interesting results and may contribute to improve the evaluation of patients with suspected COVID-19 infection, especially in the pre-hospital setting. However, external validation of our score is still needed.

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