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CHEST

Early Recognition of Low-Risk SARS-CoV-2 Pneumonia

A Model Validated With Initial Data and Infectious Diseases Society of America/American Thoracic Society Minor Criteria

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BACKGROUND: A shortage of beds in ICUs and conventional wards during the COVID-19 pandemic led to a collapse of health care resources.

RESEARCH QUESTION: Can admission data and minor criteria by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) help identify patients with low-risk SARS-CoV-2 pneumonia?

STUDY DESIGN AND METHODS: This multicenter cohort study included 1,274 patients in a derivation cohort and 830 (first wave) and 754 (second wave) patients in two validation cohorts. A multinomial regression analysis was performed on the derivation cohort to compare the following patients: those admitted to the ward (assessed as low risk); those admitted to the ICU directly; those transferred to the ICU after general ward admission; and those who died. A regression analysis identified independent factors for low-risk pneumonia. The model was subsequently validated.

RESULTS: In the derivation cohort, similarities existed among those either directly admitted or transferred to the ICU and those who died. These patients could, therefore, be merged into one group. Five independently associated factors were identified as being predictors of low risk (not dying and/or requiring ICU admission) (ORs, with 95% CIs): peripheral blood oxygen saturation/F_{IO_2} > 450 (0.233; 0.149-0.364); < 3 IDSA/ATS minor criteria (0.231; 0.146-0.365); lymphocyte count > 723 cells/mL (0.539; 0.360-0.806); urea level < 40 mg/dL (0.651; 0.426-0.996); and C-reactive protein level < 60 mg/L (0.454; 0.285-0.724). The areas under the curve were 0.802 (0.769-0.835) in the derivation cohort, and 0.779 (0.742-0.816) and 0.801 (0.757-0.845) for the validation cohorts (first and second waves, respectively).

INTERPRETATION: Initial biochemical findings and the application of < 3 IDSA/ATS minor criteria make early identification of low-risk SARS-CoV-2 pneumonia (approximately 80% of hospitalized patients) feasible. This scenario could facilitate and streamline health care resource allocation for patients with COVID-19. CHEST 2022; 162(4):768-781

KEY WORDS: COVID-19; IDSA/ATS; pneumonia; risk profiling; SARS-CoV-2

ABBREVIATIONS: ATS = American Thoracic Society; AUC = area under the receiver-operating characteristic curve; CAP = community-acquired pneumonia; CRP = C-reactive protein; DD = D-dimer; IDSA = Infectious Diseases Society of America; NPV = negative predictive value; PPV = positive predictive value; Spo_2 = peripheral blood oxygen saturation

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Take-home Points

Study Question: Can admission data and IDSA/ATS minor criteria help identify patients with low-risk SARS-CoV-2 pneumonia not requiring ICU admission or who will die during hospitalization?

Results: Five independent factors predicted low-risk SARS-CoV-2 pneumonia: $Spo_2/Fio_2 > 450$; < 3 IDSA/ATS minor criteria; lymphocyte count > 723 cells/mL; urea level < 40 mg/dL; and CRP level < 60 mg/L.

Interpretation: Approximately 80% of hospitalized patients with COVID-19 have low-risk pneumonia and are identifiable with data made available upon admission.

COVID-19 caused by SARS-CoV-2 spread rapidly worldwide, leading the World Health Organization to declare a pandemic in March 2020. The clinical course of COVID-19 varies. In approximately 80% of infections, disease is mild; however, in more severe cases, 10% to 15% of infections require hospitalization while 5% require ICU admission.[1-3] Health systems have often become overwhelmed due to a shortage of hospital and ICU beds with respect to the number of patients in need of such. This strain on health care resources is extensive and has raised a major concern during the pandemic.[4-6] As it relates to ICU admission more specifically, patients may either require direct ICU admission due to severe presentation of COVID-19 or an eventual transfer to the ICU from a conventional ward due to clinical worsening or disease progression. There are limited data on the clinical profiles of these patient subsets.

Although several ongoing studies aim to obtain a comprehensive picture of immune[7] and inflammatory host responses and the viral load to determine disease severity and prognosis,[8–11] there are some issues. It is not currently feasible to assess such variables in the ED, and there are no specific ICU admission criteria for COVID-19. In the latter case, many clinicians use scores to predict mortality and disease progression.[12-17] However, the ability to triage patients per ward allocation using initial data from the ED could prove significant, facilitating early identification of low-risk COVID-19 pneumonia that will either not require a later ICU transfer or result in death.

In other words, successive pandemic waves could continue witnessing health care institutions exceeding their capacity. Early identification may address the issue of a fair use of health care resources and promote the safe and prompt re-direction of patients deemed suitable to wards, home hospitalization, field hospitals, or medicalized hotels requiring less complex resources.[5]

We hypothesized that a combination between clinical and biochemical analysis data obtained at the ED and the minor criteria for ICU admission set forth by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) could help differentiate between low-risk and severe COVID-19 pneumonia (leading to death or requiring ICU admission).[18] We also hypothesized that patients either transferred from the ward to the ICU or those who die may share some similarities regarding disease severity as those directly admitted to the ICU owing to an underestimation of their conditions.

The primary aim of the current study was to identify factors for low-risk SARS-CoV-2 pneumonia that will not require ICU admission (directly or transferred from the ward) or lead to death during hospitalization, with the use of clinical and biochemical data obtained in the ED and the IDSA/ATS minor criteria for ICU admission in community-acquired pneumonia (CAP). The model was also validated in patients from the second COVID-19 wave. We thus had two secondary aims: (1) to compare the initial characteristics of patients directly admitted to the ICU and those either transferred to the ICU from the ward or dying from COVID-19 during hospitalization; and (2) to validate the study model in patients from the second COVID-19 wave.

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The data sets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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Study Design and Methods

Study Design

The Transparent Reporting of Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) Statement for the reporting of studies developing, validating, or updating prediction models, whether for diagnostic or prognostic purposes, was followed (see the Supplemental File for the checklist).[19] This was a multisite study of derivation and validation cohorts across several Spanish hospitals that involved patients from the first and second COVID-19 waves. We included patients with clinical symptoms and a microbiologically confirmed diagnosis of SARS-CoV-2 according to reverse transcription polymerase chain reaction testing performed on nasopharyngeal swabs. However, patients transferred from other medical facilities or nursing homes were excluded.

The study Biomedical Research Ethics Committee of La Fe University and Polytechnic Hospital (2020-122-1) approved the study for the derivation cohort, and the Ethics Committee of Galicia (Code 2020/239) approved the study for the validation cohort. The need for written informed consent was waived due to the noninterventional study design.

Data Collection

The following data were collected: demographic characteristics, smoking or alcohol habits, number of days from symptom onset, comorbidities (hypertension, cardiovascular disease, obesity, liver or renal disease, and chronic respiratory disease such as COPD or asthma), and immunosuppression due to malignancy, transplantations, or any immunosuppressive therapy. Initial blood levels were recorded for biochemistry, creatinine, aspartate transaminase, lactate dehydrogenase, D-dimer (DD), C-reactive protein (CRP), and WBC counts (including absolute neutrophil, lymphocyte, and platelet counts). Oxygen saturation measurements of room air and/or blood gas analysis results were recorded, and peripheral blood oxygen saturation (Spo_2)/Fio_2 ratios were calculated.[20] Initial chest radiographic findings were recorded as unilobar or multilobar ($\geq$ 2 lobes) infiltrates. Initial assessments of disease severity were conducted by calculating the CURB-65 score (which indicates confusion, urea, respiratory rate, BP, age $\geq$ 65 years)[21] and using the IDSA/ATS minor criteria for ICU admission.[18]

Multisite Derivation Cohort

Patients admitted to four Spanish hospitals (La Fe University and Polytechnic Hospital in Valencia; Cruces University Hospital in Barakaldo; Galdakao-Usansolo Hospital in Galdacano; and Hospital Clinic of Barcelona) between March and May 2020 were recruited. The derivation cohort was divided into three subsets: (1) patients admitted to a ward who were discharged alive and did not require an ICU transfer; (2) those admitted to a ward who died or required ICU transfer; and (3) those admitted directly to the ICU from the ED or within 24 h of hospital admission.

Multisite Validation Cohorts

The first validation cohort comprised patients from across eight hospitals in Galicia who were diagnosed between March 1, 2020, and April 24, 2020, during the first COVID-19 wave. The second validation cohort included patients recruited from across three Spanish hospitals (La Fe University and Polytechnic Hospital in Valencia; Cruces University Hospital in Barakaldo; and Galdakao-Usansolo Hospital in Galdacano) who were diagnosed between August 1, 2020, and November 30, 2020, during the second COVID-19 wave. Each cohort was divided into two subsets: (1) patients admitted to a ward who were discharged alive and did not require an ICU transfer; and (2) patients who died or required ICU admission.

Statistical Analysis

The statistical analysis was performed by using IBM SPSS version 25.0 (IBM SPSS Statistics, IBM Corporation), with a P value $< .05$ being considered statistically significant. Qualitative variables were compared with the χ^2 test, and quantitative variables were compared with the analysis of variance or Kruskal-Wallis test. One-way analysis of variance or Kruskal-Wallis tests were used for comparisons of more than two groups. Age was stratified into three groups: $<$ 50 years, 50 to 70 years, and $>$ 70 years.

Blood results are expressed as medians with the interquartile range. For the multivariate analyses, these results were stratified by using the following thresholds obtained from the cohort medians and/or by considering previous data: DD $>$ 1,000 ng/mL or urea $>$ 40 mg/dL (medians in the current cohort); CRP $\geq$ 60 mg/L (as reported in previous studies and the median in the subset of patients admitted to a ward); Spo_2/Fio_2 $\leq$ 450 (median in the subset of patients admitted to a ward); and an absolute lymphocyte count $<$ 724 cells/mL (very close to the median in the subset of patients admitted to a ward; this cutoff has also been validated by our group as an independent risk factor for death in pneumonia).[22] Radiographic pulmonary infiltrates were grouped as either unilobar or multilobar. Finally, we dichotomized both the IDSA/ATS minor criteria ($<$ 3 or $\geq$ 3) and the number of days of symptoms ($<$ 7 or $\geq$ 7 days).[23] The following steps were taken. First, we performed a multinomial stepwise logistic regression analysis on the derivation cohort to compare the three patient subsets (ward, ICU direct, and ICU transfer plus death) and estimate significantly independent variables. The subset of patients admitted to a ward was the reference group. The model included independent variables found to be either significant in univariate analyses or deemed clinically relevant: hypertension, cardiovascular diseases, age, the Spo_2/Fio_2 ratio, urea concentrations, CRP levels, lymphocyte counts, DD levels, IDSA/ATS minor criteria, and number of days of symptoms. To avoid overfitting, a step-by-step variable selection (conditional method) was performed to detect collinearity.

Second, we completed a binary logistic regression analysis to predict low-risk (ward admitted) vs high-risk (ICU admission directly from the ED or ward) SARS-CoV-2 pneumonia and/or death (by merging these two subsets). We adjusted for independent variables found to be significant in any of the logits of the prior multinomial analysis. Model calibration was then assessed by using the Hosmer-Lemeshow test (the distance between the observed and expected values). The area under the receiver-operating characteristic curve (AUC) was also calculated.

Third, in the validation cohort, we evaluated performance of those factors associated with low-risk SARS-CoV-2 pneumonia in the regression logistic analysis conducted of the derivation cohort and calculated corresponding AUCs.

TABLE 1] Baseline Characteristics of the Derivation Cohort

Characteristic	Data Availability (N = 1,274)	Ward (n = 915)	Direct ICU Admission (n = 128)	ICU Transfer From vthe Ward + Deaths in the Ward (n = 231)
Demographics				
Age, y	1,274	61 (50-72)	61 (49-70)	70 (59-80)
Male sex	1,274	534 (58.4)	91 (71.1)	170 (73.6)
Current or former smokers	1,237	306 (34.6)	37 (29.4)	66 (29.2)
Comorbidities				
Hypertension	1,274	378 (41.3)	57 (44.5)	127 (55)
Diabetes	1,273	155 (17)	32 (25)	56 (24.2)
Dyslipidemia	1,274	327 (35.7)	40 (31.3)	102 (44.2)
Chronic heart disease	1,274	128 (14)	20 (15.6)	59 (25.5)
Chronic renal disease	928	47 (7.2)	9 (8.6)	25 (14.6)
Chronic liver disease	1,274	22 (2.4)	5 (3.9)	10 (4.3)
Cancer history	929	51 (7.8)	8 (7.5)	20 (11.7)
Chronic respiratory disease	1,274	185 (20.2)	26 (20.3)	53 (22.9)
Symptoms				
Days since symptom onset	1,268			
No. of days since symptom onset		7 (5-10)	7 (5-9)	6 (4-8)
< 7 Days since symptom onset		344 (37.7)	53 (42.1)	118 (51.5)
Radiologic findings				
Multilobar infiltrates	1,252	624 (68.99)	106 (86.9)	179 (79.6)
Severity				
Spo_2/Fio_2 ratio at admission	1,258	457.1 (447.6-461.9)	423.8 (309.5-447.6)	442.9 (419.1-457.1)
CURB-65 score	1,252	1 (0-1)	1 (1-2)	1 (1-2)
≥ 3 IDSA/ATS minor criteria	1,272	80 (8.8)	44 (34.4)	70 (30.3)
Biochemical parameters at admission				
Urea, mg/dL	1,027	31 (24-41)	41 (31-60)	41 (29-61)

(Continued)

TABLE 1] (Continued)

Characteristic	Data Availability (N = 1,274)	Ward (n = 915)	Direct ICU Admission (n = 128)	ICU Transfer From vthe Ward + Deaths in the Ward (n = 231)
LDH, UI/L	1,064	280 (230-354)	434 (354-590)	349.5 (276-449.5)
C-reactive protein, mg/L	1,265	58.1 (25.8-112.7)	135.6 (81.3-228.1)	96.3 (56.5-171.3)
D-dimer, ng/mL	1,096	640 (400-1,114)	930 (600-2,020)	900 (500-1,630)
Leukocyte count, cells/mL	1,261	6,140 (4,700-8,090)	7,430 (6,555-11,350)	6,320 (4,740-8,780)
Neutrophil count, cells/mL	1,272	4,505 (3,210-6,200)	6,340 (4,100-10,000)	4,800 (3,490-7,250)
Lymphocyte count, cells/mL	1,273	980 (720-1,300)	780 (530-1,140)	770 (530-1,090)
Platelet count, cells/mL	1,270	187,000 (148,000-242,000)	215,000 (169,000-261,000)	170,000 (129,000-213,000)
Outcomes				
In-hospital mortality	1,274	NA	29 (22.7)	127 (55)

Data are expressed as median (interquartile range [IQR]) or No. (%). CURB-65 = confusion, respiratory rate, BP, age ≥ 65 years; IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; LDH = lactate dehydrogenase; NA = not applicable; Spo_2 = peripheral blood oxygen saturation.

Results

Patient Characteristics

The derivation cohort included 1,274 patients (excluding 94 from nursing homes). The first validation cohort comprised 830 patients (excluding 105 from nursing homes), and the second validation cohort comprised 754 patients (excluding 19 from nursing homes). In-hospital mortality occurred in 156 (12.2 %) patients from the derivation cohort: 92 (9.1%) comprised those treated in wards; 29 (22.7%), those directly admitted to the ICU; and 35 (25.2%), those transferred to the ICU later (e-Table 1). There were 122 (14.7%) deaths in the first validation cohort and 54 (7.1%) in the second validation cohort.

Univariate and Multivariate Analyses in the Derivation Cohort

Univariate Analysis: Table 1 presents the demographic characteristics, comorbidities, and initial biochemical results of the three patient subsets. One hundred twenty-eight patients were initially admitted to the ICU, and 139 were transferred to the ICU after being admitted to a ward. For the analysis, patients who died were included in the subset of those requiring an eventual transfer to the ICU. The ICU group had a higher proportion of comorbidities, mainly cardiovascular diseases and cardiovascular risk factors. The laboratory analysis revealed lower lymphocyte and platelet counts in the ICU direct group compared with the ward and ICU transfer plus death groups.

Multivariate Analyses: Figure 1 presents results for the two logit models obtained in the multinomial regression analysis, compared with the ward admission reference group. Model 1 compared the ICU direct and ward groups, and Model 2 compared the ICU transfer plus deaths and ward groups. The independent variables were set as age, sex, cardiovascular disease, arterial hypertension, time since symptom onset, IDSA/ATS minor criteria, the Spo_2/Fio_2 ratio, urea concentration, CRP level, lymphocyte count, and DD level. Three independent factors were found to have similar ORs for three predictive factors in both cohorts; namely, $Spo_2/Fio_2 \leq 450$; the presence of < 3 IDSA/ATS minor criteria; and CRP level < 60 mg/L. The lymphocyte count was relevant only in Model 2.

After confirming similar predictors and ORs in the two comparator groups (ICU direct vs ICU transfer or death), the whole cohort was stratified into two subsets: patients admitted to a ward and discharged alive

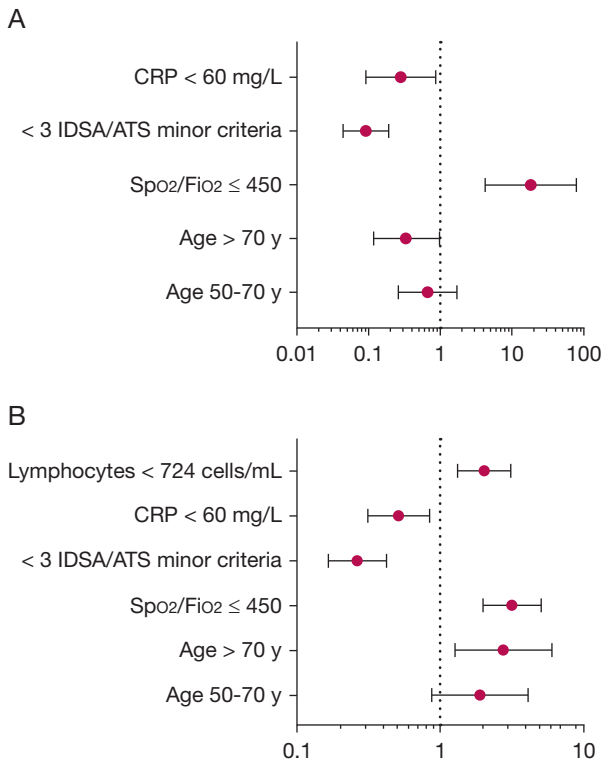

Figure 1 – *Multinomial regression analysis results presented as OR and 95% CI for the two logit models: direct ICU admission (A) and ICU transfer from ward + deaths (B). Ward admission is used as the reference category. CRP = C-reactive protein; IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; Spo_2 = peripheral blood oxygen saturation.*

(considered as low-risk) vs any ICU admission and/or death (Table 2). The regression logistic analysis identified five independent variables (Table 3)—Spo_2/Fio_2 ratio ≤ 450, ≥ 3 IDSA/ATS minor criteria, lymphocyte count < 724 cells/mL, urea level > 40 mg/dL, and CRP level ≥ 60 mg/L—adjusted by DD level, number of days since symptom onset, and two comorbidities (hypertension and cardiovascular diseases). The Hosmer-Lemeshow test showed a χ^2 value of 4.316 and a *P* value of .743. The model AUC was 0.802 (95% CI, 0.769-0.835; *P* < .001) (Fig 2), with a sensitivity and specificity of 85.9% and 55.6%, respectively, and a positive predictive value (PPV) and a negative predictive value (NPV) of 87.2% and 52.8%. We performed the same analysis, including CURB-65 in the model instead of the IDSA/ATS minor criteria, and obtained a worse performance of the model (e-Table 2).

The estimated probability of low-risk pneumonia by the number of factors found in the regression analysis ranged from 97.1% (when all five were fulfilled) to 22.5% to 30.8% (when two or less were fulfilled) (Fig 3A). Nomograms have been provided in Figure 3B and Figure 3C for better risk identification under different scenarios.

Univariate and Multivariate Analyses in the Validation Cohorts

First Validation Cohort: Table 2 details the demographic characteristics, comorbidities, and initial biochemical results of the two validation cohort groups. Compared with the derivation cohort, comorbidities were similar; however, patients had fewer multilobar infiltrates and lower CRP levels. Table 4 details the IDSA/ATS minor criteria. Table 3 shows that the independent variables behaved like those of the derivation cohort, with comparable ORs. The AUC was 0.779 (95% CI, 0.742-0.816; *P* < .001) (Fig 2), with a sensitivity and specificity of 84.2% and 53.6%, respectively, and a PPV and NPV of 84.9% and 52.3%.

Second Validation Cohort: The second validation cohort presented similar demographic characteristics, comorbidities, analytical parameters, and IDSA/ATS minor criteria (Tables 2, 4). The same independent variables were identified as in the other two cohorts, with the exception of urea, which did not enter the model (Table 3). The AUC was 0.801 (0.757-0.845; *P* < .001), with a sensitivity and specificity of 89.5% and 50%, respectively, and a PPV and NPV of 92% and 42.2%.

Discussion

In summary, approximately 80% of patients hospitalized with COVID-19 had low-risk pneumonia (discharged alive and did not require ICU admission) after being admitted to a conventional ward. Five factors were identified during the initial ED evaluation that would predict no ICU requirement or death (ie, low-risk pneumonia; AUC, 0.802): IDSA/ATS minor criteria, Spo_2/Fio_2 ratio, CRP level, lymphocyte count, and urea level. These factors were validated in both a different multicenter cohort (AUC, 0.779) and in patients from the second COVID-19 wave (AUC, 0.801). Given that the scale of the pandemic has led to shortages of hospital beds, it is crucial to have simple criteria to improve the safe triage of both mild and severe episodes of pneumonia and ensure better, appropriate allocation of resources.

In the current study, 71.8% of the patients in the derivation cohort (75.3% and 86.5% in the first and second validation cohorts, respectively) were admitted to a conventional ward and remained there until discharged alive. Only 10.1% required direct ICU admission, whereas 18.1% either died or were later

TABLE 2] Ward-Admitted Patients and ICU-Admitted/Deceased Patients in the Derivation and Validation Cohorts

Characteristic	Derivation Cohort			Validation Cohort: First Wave			Validation Cohort: Second Wave		
	Data Availability (N = 1,274)	Ward (n = 915)	ICU and/or Death (n = 359)	Data Availability (n = 830)	Ward (n = 625)	ICU and/or Death (n = 205)	Data Availability (n = 754)	Ward (n = 652)	ICU and/or Deaths (n = 102)
Demographics									
Age, y	1,274	61 (50-72)	66 (55-76)	830	68 (56-76)	74 (67-84)	754	58 (47-70)	67 (55-80)
Male sex	1,274	534 (58.4)	261 (72.7)	830	350 (56)	136 (66.3)	754	372 (57.1)	72 (70.6)
Current or former smokers	1,237	306 (34.6)	103 (29.3)	618	158 (35.6)	67 (38.5)	728	206 (32.9)	43 (44.3)
Comorbidities									
Hypertension	1,274	378 (41.3)	184 (51.3)	830	269 (43)	125 (61)	754	222 (34)	54 (52.9)
Diabetes	1,273	155 (17)	88 (24.5)	830	101 (16.2)	57 (27.8)	754	101 (15.5)	34 (33.3)
Dyslipidemia	1,274	327 (35.7)	142 (39.6)	827	224 (36)	78 (38)	754	202 (31)	38 (37.3)
Chronic heart disease	1,274	128 (14)	79 (22)	830	100 (16)	67 (32.7)	754	86 (13.2)	30 (29.4)
Chronic renal disease	928	47 (7.2)	34 (12.3)	830	31 (5)	22 (10.7)	754	43 (6.6)	14 (13.7)
Chronic liver disease	1,274	22 (2.4)	15 (4.2)	830	22 (3.5)	8 (3.9)	754	27 (4.1)	14 (13.7)
Cancer history	929	51 (7.8)	28 (10.1)	830	40 (6.4)	23 (11.2)	754	48 (7.4)	12 (11.8)
Chronic respiratory disease	1,274	185 (20.2)	79 (22)	830	99 (15.8)	32 (15.6)	754	134 (20.6)	31 (30.4)
Symptoms									
Days since symptom onset (IQR)	1,268			807			610		
Median no. of days since symptom onset		7 (5-10)	7 (4-8)		7 (4-10)	7 (3-9)		7 (4-9)	5 (3-7)
< 7 Days since symptom onset		344 (37.7)	171 (48.2)		253 (41.4)	96 (49)		231 (44.2)	60 (73.2)

(Continued)

TABLE 2] *(Continued)*

Characteristic	Derivation Cohort			Validation Cohort: First Wave			Validation Cohort: Second Wave		
	Data Availability (N = 1,274)	Ward (n = 915)	ICU and/or Death (n = 359)	Data Availability (n = 830)	Ward (n = 625)	ICU and/or Death (n = 205)	Data Availability (n = 754)	Ward (n = 652)	ICU and/or Deaths (n = 102)
Radiologic findings				830					
Multilobar infiltrates	1,252	624 (68.9)	285 (82.1)		225 (36)	84 (41)	750	437 (67.4)	75 (73.5)
Severity									
Spo_2/Fio_2 ratio at admission	1,258	457.1 (447.6-461.9)	438.1 (404.8-454.8)	826	452.4 (442.9-457.1)	423.8 (361.9-447.6)	754	457.1 (447.6-461.9)	438.1 (381-452.4)
≥ 3 IDSA/ATS minor criteria	1,272	80 (8.8)	114 (31.8)	830	86 (13.8)	90 (43.9)	366	28 (8.8)	16 (36.4)
Biochemical parameters at admission									
Urea, mg/dL	1,027	31 (24-41)	41 (30-61)	828	35 (28-45)	50 (36-72)	752	31 (24-41)	44 (30-65)
LDH, UI/L	1,064	280 (230-354)	388 (300-489)	734	320 (237-463)	417 (324-650)	682	269 (216-333)	350 (270-469)
C-reactive protein, mg/L	1,265	58.1 (25.8-112.7)	109 (61-184.1)	808	29.4 (7.9-81)	76.1 (18.7-148)	754	49.6 (21.1-104)	127 (60.5-162.8)
D-dimer, ng/mL	1,096	640 (400-1,104)	910 (537-1,802)	662	613 (410-1,069)	854 (579-1,636)	715	560 (370-890)	905 (560-1,660)
Leukocyte count, cells/mL	1,261	6,140 (4,700-8,090)	6,770 (4,970-9,690)	830	5,480 (4,320-7,290)	6,100 (4,550-8,750)	752	5,830 (4,600-7,660)	6,840 (4,890-8,700)
Neutrophil count, cells/mL	1,272	4,505 (3,210-6,200)	5,255 (3,600-8,100)	760	3,770 (2,900-5,540)	4,800 (3,310-7,200)	752	4,190 (3,090-5,700)	5,435 (3,460-7,390)
Lymphocyte count, cells/mL	1,273	980 (720-1,300)	770 (530-1,100)	823	990 (700-1,360)	780 (510-1,020)	752	1,060 (790-1,420)	770 (580-1,040)
Platelet count, cells/mL	1,270	187,000 (148,000-242,000)	185,000 (135,000-237,000)	825	179,000 (138,000-233,000)	164,000 (128,000-211,000)	752	196,000 (153,000-248,000)	170,000 (128,000-229,000)

Data are summarized as No. (%) or median (interquartile range). IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; LDH = lactate dehydrogenase; NA = not applicable; Spo_2 = peripheral blood oxygen saturation.

TABLE 3] Regression Logistic Analysis to Identify Predictive Factors for Non-ICU Admission and/or Death in the Derivation and Validation Cohorts

Variable	Derivation Cohort			Validation Cohort: First Wave			Validation Cohort: Second Wave		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
$Spo_2/Fio_2 \leq 450$	0.233	0.149-0.364	< .001	0.281	0.171-0.463	< .001	0.377	0.203-0.700	.002
≥ 3 IDSA/ATS minor criteria	0.231	0.146-0.365	< .001	0.340	0.211-0.548	< .001	0.360	0.179-0.723	.004
Lymphocytes < 724 cells/mL	0.539	0.360-0.806	.003	0.609	0.392-0.947	.028	0.553	0.305-0.995	.049
Urea > 40 mg/dL	0.651	0.426-0.996	.048	0.562	0.353-0.896	.016	…	…	…
CRP ≥ 60 mg/L	0.454	0.285-0.724	.001	0.654	0.421-1.015	.058	0.249	0.127-0.487	< .001

CRP = C-reactive protein; IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; Spo_2 = peripheral blood oxygen saturation.

transferred to the ICU. The derivation and validation cohorts presented with ages and comorbidity features similar to those previously reported.[3] Mortality rates were 12.2%, 14.7%, and 7.1% in the derivation cohort and first and second validation cohorts, indicating lower mortality during the second wave.

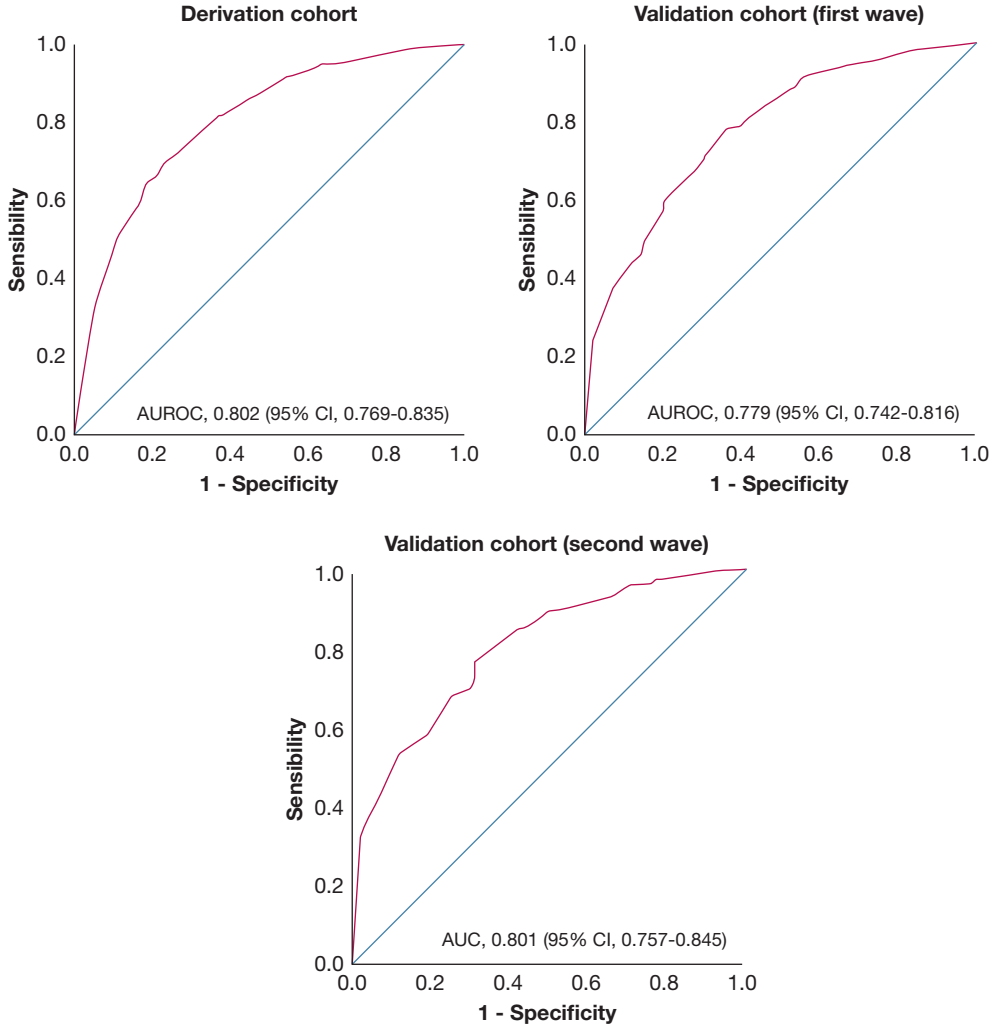

Figure 2 – *AUROC values for the derivation and validation cohorts. AUROC = area under the receiver-operating characteristic curve.*

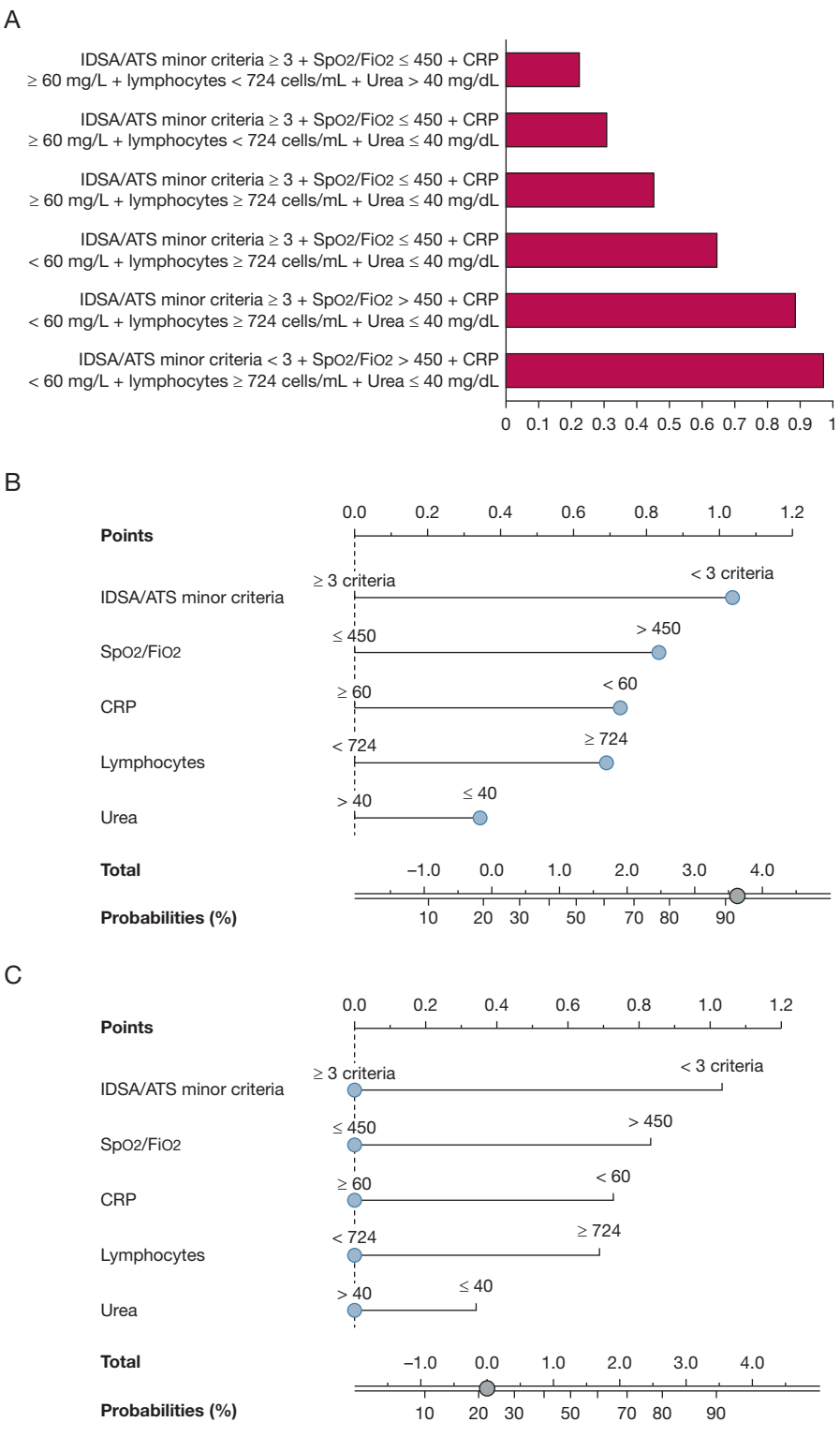

Figure 3 – *A, Estimated probabilities of low-risk pneumonia according to the number of predictive factors that are met. B, Nomogram in the best clinical scenario. C, Nomogram in the worst clinical scenario. Instructions for the interpretation of nomograms: locate the patient's IDSA/ATS criteria number on the IDSA/ATS minor criteria axis. Draw a line straight upward to the points axis to determine how many points toward the probability of nonclinical deterioration the patient receives for his or her criteria number. Repeat the process for each variable. Sum the points achieved for each of the predictors. Locate the final sum on the total axis. Draw a line straight down to find the patient's probability nonclinical deterioration (ICU admission or death). In the figure, maximum probability of nonclinical deterioration is marked on the probabilities axis (91%) corresponding to a patient with all the characteristics in the right-side category (dots in blue). CRP = C-reactive protein; IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; Spo_2 = peripheral blood oxygen saturation/ Fio_2.*

Using a multinomial regression, we compared the two subsets of severely ill patients (ICU direct admissions and later ward transfers to the ICU or deaths) in relation to patients in the ward. Both groups of severely ill patients exhibited similarities compared with ward patients: more male subjects, more cardiovascular diseases, lower Spo_2/Fio_2ratios, lower lymphocyte counts, and higher urea, lactate dehydrogenase, DD, and CRP levels. They also both presented with ≥ 3 IDSA/ATS minor criteria (34.4% and 30.3%) in the ED.

TABLE 4] IDSA/ATS Minor Criteria for Derivation and Validation Cohorts

Variable	Derivation Cohort				Validation Cohort: First Wave				Validation Cohort: Second Wave			
	Data Availability (n = 1,272)	Ward (n = 913)	ICU and/or Deaths (n = 359)	*P* Value	Data Availability (n = 830)	Ward (n = 625)	ICU and/or Deaths (n = 205)	*P* Value	Data Availability (n = 754)	Ward (n = 652)	ICU and/or Deaths (n = 102)	*P* Value
Confusion	1,269	22 (2.4)	24 (9.6)	< .001	830	16 (2.6)	18 (8.8)	< .001	754	16 (2.5)	12 (11.8)	< .001
RR ≥ 30	935	17 (2.6)	86 (30.8)	< .001	692	17 (3.2)	49 (29.3)	< .001	373	22 (6.7)	10 (21.7)	.001
$Pao_2/Fio_2 \leq 250$ (or room air $Spo_2 < 90\%$)	1,264	51 (5.6)	94 (26.7)	< .001	826	45 (7.2)	85 (41.7)	< .001	754	35 (5.4)	23 (22.5)	< .001
BUN ≥ 20 mg/dL (urea > 42 mg/dL)	1,026	182 (22.9)	106 (45.9)	< .001	828	185 (29.7)	130 (63.4)	< .001	752	165 (25.4)	59 (57.8)	< .001
Multilobar infiltrates	1,196	620 (72.5)	283 (83.0)	< .001	830	474 (75.8)	183 (89.3)	< .001	750	437 (67.4)	75 (73.5)	.219
Leukopenia (< 4,000 cells/mL)	1,255	127 (14.1)	44 (12.5)	.453	830	109 (17.4)	35 (17.1)	.904	752	89 (13.7)	11 (10.8)	.421
Thrombocytopenia (platelet count < 100,000/mL)	1,268	32 (3.5)	25 (7.0)	.007	825	39 (6.3)	23 (11.3)	.018	752	22 (3.4)	11 (10.8)	.001
Hypothermia ($T^a < 36°C$)	1,268	88 (9.7)	37 (10.9)	.525	824	61 (9.8)	16 (8)	.438	749	51 (7.9)	7 (7)	.765
Hypotension requiring active fluid resuscitation	1,241	10 (1.1)	10 (3.0)	.019	828	8 (1.3)	7 (3.4)	.046	753	7 (1.1)	5 (5)	.004

IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; RR = respiratory rate.

Indeed, the independent risk was identical for three factors, allowing the two subsets of severely ill patients to be merged for later analyses and validation. The findings regarding the IDSA/ATS minor criteria are interesting, as patients initially admitted to a ward with ≥ 3 criteria faced a higher risk of a later transfer to the ICU or death. This outcome could suggest that disease severity of these patients could be insufficiently recognized. In CAP, as validated elsewhere, the presence of ≥ 3 IDSA/ATS minor criteria indicates a requirement for ICU admission in those patients who do not need mechanical ventilation or vasopressor treatment.[23,24] To our knowledge, however, the IDSA/ATS minor criteria have not been evaluated for identifying severe episodes of COVID-19. We also independently assessed two parameters that provide biological information similar to those used in this study (the Pao_2/Fio_2 ratio compared with the Spo_2/Fio_2 ratio and BUN compared with urea), which are more widely used in EDs, and applied thresholds obtained from our cohort and frequently used in literature.

In SARS-CoV-2 disease, low-risk pneumonia has required the greatest use of hospital resources and bed occupancy per day. It is therefore vital that patients with such cases are quickly differentiated from those with more severe cases in EDs. This can be accomplished promptly by using five independent predictive factors adjusted for age, hypertension, comorbidities, and other biochemical findings. The model obtained in this study has a good discriminating ability to identify these patients. AUC values were 0.802 and 0.779 in the derivation and validation cohorts, respectively, and the model showed similar sensitivity, specificity, and predictive values. Although urea was not entered as an independent variable for patients from the second COVID-19 wave, the model was also validated in this group, with an AUC of 0.801, proving its robustness.

Four biochemical variables independently predicted low-risk pneumonia: lymphocyte count ≥ 724 cells/mL; urea level < 40 mg/dL; Spo_2/Fio_2 ratio > 450; and CRP level < 60 mg/L. Interestingly, urea was only an independent variable during the first wave. This may be because patients admitted to a ward during the second wave tended to be younger and present lower urea levels compared with patients from the first wave. The presence of lymphopenia has been reported in severe cases. Yang et al[25] found that up to 85% of severely ill patients presented lymphopenia, which has since been considered a signature of severe disease[26] and immunologic misfiring.[27] Huang et al[2] and Liu et al[28] reported the importance of initial lymphocyte counts and their evolution during the course of infection. In the current study, we selected a threshold (< 724 cells/mL) that has been associated with higher mortality in CAP.[22,29] The reasons for lymphopenia are not clear, although a direct toxic action against lymphocytes resulting in their apoptosis or necrosis is possible. Indeed, reductions in lymph nodes have been noted in some autopsies. Another important aspect is the possible endothelial dysfunction triggered by SARS-CoV-2.[26] Low initial CRP levels (< 60 mg/L) independently predicted the lack of requirement for ICU admission or progression to death. Higher CRP levels, with thresholds ranging from 40 to 100 mg/L, have been associated with poor prognosis. Castro et al[30] highlighted that CRP levels as a laboratory result could estimate mortality.

Although this study has several strengths, such as the inclusion of three multicenter cohorts and double validation in different disease waves, important limitations must be considered. First, some variables were missing, and there were potential differences in ICU strategies among hospitals. However, we did exclude patients from nursing homes where therapeutic effort could have been limited.[31] Second, a biochemical analysis was performed only at admission and did not include dynamic monitoring.[28] The current study was performed when the population was not vaccinated. Similarly, a subset of nonadmitted patients was excluded.

Interpretation

A combination of parameters, including host response (eg, lymphocyte count, CRP levels), lung function (eg, the Spo_2/Fio_2 ratio), and < 3 IDSA/ATS minor criteria, provides a feasible tool for decision-making processes in the ED as it relates to evaluating disease severity for safe triage and resource allocation. Similarities with some initial analytical results and IDSA/ATS criteria existed in patients admitted directly to the ICU and those who were either transferred to the ICU from the ward or died during ward hospitalization. Early identification of patients with low-risk SARS-CoV-2 pneumonia who will not require ICU admission and/or progress to death could help with resource allocation during periods of hospital bed shortages.

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Additional information: The e-Tables are available online under "Supplementary Data."

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