Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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

Rosario Menéndez, MD, PhD; Raúl Méndez, MD, PhD; Paula González-Jiménez, MD; Rafael Zalacain, MD, PhD; Luis A. Ruiz, MD; Leyre Serrano, MD; Pedro P. España, MD, PhD; Ane Uranga, MD, PhD; Catia Cillóniz, PhD; Luis Pérez-de-Llano, MD, PhD; Rafael Golpe, MD, PhD; and Antoni Torres, MD, PhD

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/FIO2 > 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.

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; SpO2 = peripheral blood oxygen saturation

AFFILIATIONS: From the Pneumology Department (R. M., R. M., and P. G.-J.), La Fe University and Polytechnic Hospital, Valencia, Spain; Respiratory Infections (R. M., R. M., and P. G.-J.), La Fe University and Polytechnic Hospital, Valencia, Spain; Respiratory Infections (R. M., R. M., and P. G.-J.), La Fe University and Polytechnic Hospital, Valencia, Spain; Medicine Department (R. M. and P. G.-J.), University of Valencia, Valencia, Spain; Center for Biomedical Research Network in Respiratory Diseases (R. M., C. C., and A. T.), University of Valencia, Valencia, Spain; Hospital Universitari La Fe, Valencia, Spain; Health Research Institute La Fe, Valencia, Spain; Department of Chest Infections, Original Research [ 162#4 CHEST OCTOBER 2022 ]

768 Original Research
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.

We hypothesized that a combination between clinical and biochemical analysis data obtained at the ED and and biochemical analysis data obtained at the ED and the IDSA/ATS 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).\(^1\)\(^8\)\(^-\)\(^1\)\(^7\) 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.\(^5\)

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.
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). 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 (SpO2/FIO2) ratios were calculated. Initial chest radiographic findings were recorded as unilobar or multilobar (≥2 lobes) infiltrates. Initial assessments of disease severity were conducted by calculating the CURB-65 score (which indicates confusion, urea, respiratory rate, BP, age) and using the IDSA/ATS minor criteria for ICU admission.

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 χ² 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 ≥ 60 mg/L (as reported in previous studies and the median in the subset of patients admitted to a ward); SpO2/FIO2 ≤ 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. Radiographic pulmonary infiltrates were grouped as either unilobar or multilobar. Finally, we dichotomized both the IDSA/ATS minor criteria (<3 or ≥3) and the number of days of symptoms (<7 or ≥7 days). 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 SpO2/FIO2 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 the 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**                                  |                               |                 |                               |                                                        |
| SPO2/FIO2 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)
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 SpO2/FIo2 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, SpO2/FIo2 ≤ 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
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, SpO2/FiO2 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 χ² 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, SpO2/FiO2 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 |
|---------------------------------------|-------------------|-------------------------------|--------------------------------|
| **Demographics**                      |                   |                               |                                |
| Age, y                                | 1,274             | 830                           | 754                            |
|                                       | 61 (50-72)        | 68 (56-76)                    | 67 (67-84)                     |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Male sex                              | 1,274             | 830                           | 754                            |
|                                       | 534 (58.4)        | 350 (56)                      | 372 (57.1)                     |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Current or former smokers             | 1,237             | 618                           | 728                            |
|                                       | 306 (34.6)        | 158 (35.6)                    | 206 (32.9)                     |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| **Comorbidities**                     |                   |                               |                                |
| Hypertension                          | 1,274             | 830                           | 754                            |
|                                       | 378 (41.3)        | 269 (43)                      | 222 (34)                       |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Diabetes                              | 1,273             | 830                           | 754                            |
|                                       | 155 (17)          | 101 (16.2)                    | 101 (15.5)                     |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Dyslipidemia                          | 1,274             | 827                           | 754                            |
|                                       | 327 (35.7)        | 224 (36)                      | 202 (31)                       |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Chronic heart disease                 | 1,274             | 830                           | 754                            |
|                                       | 128 (14)          | 100 (16)                      | 86 (13.2)                      |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Chronic renal disease                 | 928               | 830                           | 754                            |
|                                       | 47 (7.2)          | 31 (5)                        | 43 (6.6)                       |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Chronic liver disease                 | 1,274             | 830                           | 754                            |
|                                       | 22 (2.4)          | 22 (3.5)                      | 27 (4.1)                       |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Cancer history                        | 929               | 830                           | 754                            |
|                                       | 51 (7.8)          | 40 (6.4)                      | 48 (7.4)                       |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| Chronic respiratory disease           | 1,274             | 830                           | 754                            |
|                                       | 185 (20.2)        | 99 (15.8)                     | 134 (20.6)                     |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| **Symptoms**                          |                   |                               |                                |
| Days since symptom onset (IQR)        | 1,268             | 807                           | 610                            |
| Median no. of days since symptom onset|                   |                               |                                |
|                                       | 7 (5-10)          | 7 (4-8)                       | 7 (4-9)                        |
|                                       | (< 7 Days since symptom onset)|               | 7 (3-9)                        |
|                                       | 344 (37.7)        | 253 (41.4)                    | 231 (44.2)                     |
|                                       | (n = 915)         | (n = 830)                     | (n = 754)                      |
| < 7 Days since symptom onset          |                   |                               |                                |

(Continued)
| Characteristic                  | Derivation Cohort | Validation Cohort: First Wave | Validation Cohort: Second Wave |
|--------------------------------|-------------------|------------------------------|--------------------------------|
|                                | Data Availability | Ward (n = 915) | ICU and/or Death (n = 359) | Data Availability | Ward (n = 625) | ICU and/or Death (n = 205) | Data Availability | Ward (n = 652) | ICU and/or Deaths (n = 102) |
| Radiologic findings            | 1,252             | 624 (68.9)      | 285 (82.1)                 | 225 (36)          | 84 (41)         | 750               | 437 (67.4)         | 75 (73.5)       |
| Multilobar infiltrates         |                   |                 | 438.1 (404.8-454.8)        | 426.1 (417.9-457.1) | 423.8 (361.9-447.6) | 754               | 457.1 (447.6-461.9) | 438.1 (381-452.4) |
| Severity                       |                   |                 |                           |                   |                 |                   |                   |                 |
| SpO2/FIO2 ratio at admission   | 1,258             | 457.1 (447.6-461.9) | 438.1 (404.8-454.8)        | 426.1 (417.9-457.1) | 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 | 1,027              | 31 (24-41)     | 41 (30-61)                  | 35 (28-45)        | 50 (36-72)       | 752              | 31 (24-41)         | 44 (30-65)      |
| Urea, mg/dL                    | 1,064             | 280 (230-354)   | 388 (300-489)               | 320 (237-463)     | 417 (324-650)    | 682              | 269 (216-333)      | 350 (270-469)   |
| LDH, UI/L                      | 1,265             | 58.1 (25.8-112.7) | 109 (61-184.1)              | 29.4 (7.9-81)     | 76.1 (18.7-148)  | 754              | 49.6 (21.1-104)    | 127 (60.5-162.8) |
| C-reactive protein, mg/L       | 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)  |
| D-dimer, ng/mL                 | 1,261             | 6,140 (4,700-8,090) | 6,770 (4,970-9,690)        | 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) |
| Leukocyte count, cells/mL      | 1,272             | 4,505 (3,210-6,200) | 5,255 (3,600-8,100)        | 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) |
| Neutrophil count, cells/mL     | 1,273             | 980 (720-1,300)  | 770 (530-1,100)             | 990 (700-1,360)   | 780 (510-1,020)  | 752              | 1,060 (790-1,420)  | 770 (580-1,040)  |
| Lymphocyte count, cells/mL     | 1,270             | 187,000 (148,000-242,000) | 185,000 (135,000-237,000) | 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; SpO2 = 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.

### 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 |
| \(\text{SpO}_2/\text{FiO}_2 \leq 450\) | 0.233 | 0.149-0.364 | < .001 | 0.281 | 0.171-0.463 | < .001 | 0.377 | 0.203-0.700 | .002 |
| \(\geq 3\) 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; \(\text{SpO}_2\) = peripheral blood oxygen saturation.

Figure 2 – AUROC values for the derivation and validation cohorts. AUROC = area under the receiver-operating characteristic curve.
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 SpO2/FIO2 ratios, 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.
| Variable                        | Derivation Cohort | Validation Cohort: First Wave | Validation Cohort: Second Wave |
|--------------------------------|-------------------|-------------------------------|--------------------------------|
|                                | Data Availability | Ward (n = 913) | ICU and/or Deaths (n = 359) | P Value | Data Availability | Ward (n = 625) | ICU and/or Deaths (n = 205) | P Value | Data Availability | 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  |
| Pao2/Fio2 ≤ 250 (or room air SpO2 < 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<sub>a</sub> < 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. 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 \( \text{PaO}_2/\text{FiO}_2 \) ratio compared with the \( \text{SpO}_2/\text{FiO}_2 \) 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; \( \text{SpO}_2/\text{FiO}_2 \) 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. found that up to 85% of severely ill patients presented lymphopenia, which has since been considered a signature of severe disease and immunologic misfiring. Huang et al. and Liu et al. 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. 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. 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. 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. Second, a biochemical analysis was performed only at admission and did not include dynamic monitoring. 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 \( \text{SpO}_2/\text{FiO}_2 \) 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.
Acknowledgments

Author contributions: R. Menéndez is the guarantor of the paper. The author contributions were as follows: conceptualization and study design, R. Menéndez; patient enrollment and database management, R. Méndez, P. G.-J., R. Z., L. A. R., L. S., P. P. E., A. U., C. C., L. P.-d.-L., R. G., and A. T.; and statistical analysis, interpretation of results, and drafting of the manuscript, R. Menéndez and R. Méndez. All authors revised the manuscript and approved the final version; all authors had full access to all of the data in the study and had the final responsibility of making the decision to submit for publication. All authors approved the final version as submitted.

Financial/nonfinancial disclosures: None declared.

Funding/support: This study was supported by Instituto de Salud Carlos III (ISCIII) through Project [COV20/00385], co-funded by the European Regional Development Fund/European Social Fund “Investing in Your Future.” R. Méndez is the recipient of the Rio Horta and Juan Rodés grants, which are supported by the Instituto de Salud Carlos III (ISCIII) (CM19/00182 and JR21/00051, respectively). P. G.-J. is the recipient of a post-resident research grant supported by the Health Research Institute La Fe [2019-053-1].

Role of sponsors: The sponsor had no role in the design of the study, data obtaining, analyses, interpretation of results, or drafting.

Other contributions: The authors thank the Integrative Research Program of Respiratory Infections of SEPAR. They also extend their thanks to Laura Descalzo, PhD, for her collaboration in the statistical analysis, as well as to Ana Latorre, PhD, and Luz Mimbiela, BS, for their help. Finally, they will always remember those who are no longer among us due to this pandemic.

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

References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324(8):782-793.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):585-594.
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-2059.
4. Wu C, Chen X, Cai Y, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-943.
5. Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of COVID-19. N Engl J Med. 2020;382(21):2049-2055.
6. Butler CR, Wong SY, Wightman AG, O’Hare AM. US clinicians’ experiences and perspectives on resource limitation and patient care during the COVID-19 pandemic. JAMA Netw Open. 2020;3(11):e2027315.
7. Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature. 2020;584(7821):463-469.
8. Laing AG, Lorenc A, Molino del Barrio J del, et al. A dynamic COVID-19 immune signature identifies associations with poor prognosis. Nat Med. 2020;26(10):1623-1635.
9. Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science. 2020;369(6508):eabc8511.
10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.
11. Bermejo-Martin JF, Gonzalez-Rivera M, Almansa R, et al. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. Crit Care. 2020;24(1):691.
12. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with Covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:c3762.
13. Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med. 2020;180(10):1081-1089.
14. Zhang JY, Lee KS, Ang LW, Leo YS, Young BE. Risk factors of severe disease and efficacy of treatment in patients infected with COVID-19: a systematic review, meta-analysis and meta-regression analysis. Clin Infect Dis. 2020;71(16):2199-2206.
15. Lin D, Zhang D, Xu J, et al. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL Score. Clin Infect Dis. 2020;71(16):1393-1399.
16. Gupta RK, Harrison EM, Ho A, et al. Development and validation of the ISARIC 4C deterioration model for adults hospitalised with COVID-19: a prospective cohort study. Lancet Respir Med. 2021;9(4):349-359.
17. Gupta RK, Marks M, Samuels THA, et al. Systematic evaluation and external validation of 22 prognostic models among hospitalised adults with COVID-19: an observational cohort study. Eur Respir J. 2020;56(6):2003498.
18. Mandell LA, Wunderink RG, Anzueto A, et al. IDSA/ATS consensus guidelines on the management of community-acquired pneumonia. Clin Infect Dis. 2007;44(suppl 2):S27-S72.
19. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162(1):55-63.
20. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the Sp02/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest. 2007;131(2):410-417.
21. Lim WS, Eerden MM van der, Laing R, et al. Defining community acquired pneumonia severity in hospitalised patients with community acquired pneumonia: an international derivation and validation study. Thorax. 2003;58(5):377-382.
22. Bermejo-Martin JF, Cilloniz C, Mendez R, et al. Lymphopenic community acquired pneumonia (L- CAP), an immunological phenotype associated with higher risk of mortality. EBioMedicine. 2017;24:231-236.
23. Chalmers JD, Taylor JK, Mandal P, et al. Validation of the Infectious Diseases Society of America/American Thoracic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients with major criteria or contraindications to intensive care unit care. Clin Infect Dis. 2011;53(6):503-511.
24. Phua J, See KC, Chan YH, et al. Validation and clinical implications of the IDSA/ATS minor criteria for severe community-acquired pneumonia. Thorax. 2009;64(7):598-603.
25. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-481.
26. Bermejo-Martin JF, Almansa R, Menendez R, Mendez R, Kelvin DJ, Torres A. Lymphopenic community acquired pneumonia as signature of severe COVID-19 infection. J Infect. 2020;80(5):e23-e24.
27. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, et al. Imbalanced host response to SARS-CoV-2 pneumonia in Wuhan, China: a systematic review, meta-analysis and meta-regression analysis. Clin Infect Dis. 2020;71(16):2199-2206.
28. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55(102763).
29. Hou H, Zhang R, Huang H, et al. Using IL-2R/lymphocyte for predicting the clinical progression of patients with
COVID-19. Clin Exp Immunol. 2020;201(1):76-84.

30. Castro V, McCoy T, Perlis R. Laboratory findings associated with severe illness and mortality among hospitalized individuals with coronavirus disease 2019 in Eastern Massachusetts. JAMA Netw Open. Preprint posted online August 28, 2020;3(10). https://doi.org/10.1001/jamanetworkopen.2020.23934

31. Dahine J, Hébert PC, Ziegler D, Chenail N, Ferrari N, Hébert R. Practices in triage and transfer of critically ill patients: a qualitative systematic review of selection criteria. Crit Care Med. 2020;48(11):e1147-e1157.