



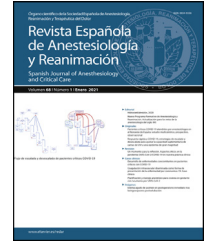
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ORIGINAL ARTICLE

C-Reactive protein and SOFA scale: A simple score as early predictor of critical care requirement in patients with COVID-19 pneumonia in Spain[☆]



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KEYWORDS

COVID-19 pneumonia;
Critical care;
C-reactive protein;
Sequential organ failure assessment - SOFA

Abstract

Objective: To identify potential markers at admission predicting the need for critical care in patients with COVID-19 pneumonia.

Material and methods: An approved, observational, retrospective study was conducted between March 15 to April 15, 2020. 150 adult patients aged less than 75 with Charlson comorbidity index ≤ 6 diagnosed with COVID-19 pneumonia were included. Seventy-five patients were randomly selected from those admitted to the critical care units (critical care group [CG]) and seventy-five hospitalized patients who did not require critical care (non-critical care group [nCG]) represent the control group. One additional cohort of hospitalized patients with COVID-19 were used to validate the score.

Measurements and main results: Multivariable regression showed increasing odds of in-hospital critical care associated with increased C-reactive protein (CRP) (odds ratio 1.052 [1.009–1.101]; $P=0.0043$) and higher Sequential Organ Failure Assessment (SOFA) score (1.968 [1.389–2.590]; $P<0.0001$), both at the time of hospital admission. The AUC-ROC for the combined model was 0.83 (0.76–0.90) (vs AUC-ROC SOFA $P<0.05$). The AUC-ROC for the validation cohort was 0.89 (0.82–0.95) ($P>0.05$ vs AUC-ROC development).

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[◇] The members of the COVID Working Group, Hospital Universitario de Salamanca-IBSAL, are presented in Appendix A.

Conclusion: Patients COVID-19 presenting at admission SOFA score ≥ 2 combined with CRP ≥ 9.1 mg/mL could be at high risk to require critical care.

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PALABRAS CLAVE

Neumonía por COVID-19;
Cuidados críticos;
Proteína C reactiva;
SOFA - evaluación de fallo orgánico secuencial

Proteína C reactiva y escala SOFA: una simple escala como factor predictivo temprano de la necesidad de cuidados críticos en los pacientes con neumonía causada por COVID-19 en España

Resumen

Objetivo: Identificar marcadores potenciales durante el ingreso que predigan la necesidad de cuidados críticos en pacientes con neumonía causada por COVID-19.

Material y métodos: Estudio autorizado, observacional y retrospectivo realizado entre el 15 de marzo y el 15 de abril de 2020; incluyó a 150 pacientes adultos menores de 75 años con índice de comorbilidad de Charlson ≤ 6 diagnosticados de neumonía por COVID-19. Se seleccionaron aleatoriamente 75 pacientes de entre los ingresados en las unidades de cuidados críticos (grupo de cuidados críticos [GC]) y 75 pacientes hospitalizados que no requirieron cuidados críticos (grupo de cuidados no críticos [GnC]) que representaron el grupo control. Se utilizó una cohorte adicional de pacientes hospitalizados con COVID-19 para validar la escala.

Medidas y resultados principales: La regresión multivariante reflejó unos incrementos de los odds ratio de cuidados críticos hospitalarios asociados al incremento de proteína C reactiva (PCR) (odds ratio: 1,052 [1,009–1,101]; $p=0,0043$) y puntuaciones en Sequential Organ Failure Assessment (SOFA) más altas (1,968 [1,389–2,590]; $p<0,0001$) en el momento del ingreso hospitalario. El valor de la curva AUC-ROC para el modelo combinado fue de 0,83 (0,76–0,90) (frente a AUC-ROC SOFA $p<0,05$). El valor de AUC-ROC para la cohorte de validación fue de 0,89 (0,82–0,95) ($p>0,05$ frente a AUC-ROC de la cohorte desarrollo).

Conclusión: Los pacientes de COVID-19 que presentan al ingreso una puntuación SOFA ≥ 2 combinada con PCR $\geq 9,1$ mg/mL podrían ser de alto riesgo a la hora de requerir cuidados críticos. © 2021 Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

A new atypical pneumonia appeared in December 2019 that was later found to be caused by a new coronavirus (SARS-CoV-2). By April 2020, the virus had spread to 212 countries worldwide, infecting more than 1,607,467 people and causing more than 98,866 deaths¹. By 9 May, 223,578 cases of infection had been diagnosed in Spain, with 26,478 related deaths². In the early stages of infection patients may experience low grade fever or flu-like symptoms, but this can also be followed by severe respiratory failure³. Patients with SARS-CoV-2 infection have high rates of hospitalization and admission to the intensive care unit (ICU)⁴. A wide range of parameters have been associated with morbidity and mortality^{3,5–8}, ranging from sex⁹ to increased plasma D dimer levels³, which may suggest endothelial activation. Many reports have also described an association between serious clinical deterioration and cytokine storm, characterized by the release of IL-6 and IL-1 type cytokines, and also by traditional inflammatory markers, such as C-reactive protein (CRP) and ferritin^{10,11}. Others suggest that severity can be predicted by different serum inflammatory profiles.

Some patients with SARS-CoV-2 infection may require critical care, and this then becomes one of the main problems faced by healthcare systems during such pandemics¹². It is still unclear what comorbidities, laboratory test results, or severity features are capable of predicting the potential need for these resources that lead to the collapse of the healthcare system. Good triage criteria and correctly identifying the profiles of high-risk patients could be the cornerstones of individualized management¹³.

In this context, we decided to evaluate our series of COVID-19 patients in order to identify markers observed at admission that could predict the need for critical care.

Material and method

Patient selection

We conducted a retrospective study collecting data from 150 patients diagnosed with COVID-19 pneumonia. All had a confirmed diagnosis of SARS-CoV-2. Seventy-five patients were randomly selected from among those admitted to the critical care units of the Salamanca University Hospital (critical

care [CC]) between 15 March and 15 April 2020. The results of an earlier pilot study in 10 patients showed that patients admitted to the critical care unit were aged under 75 years and had a Charlson comorbidity index¹⁴ of under 6. Therefore, we selected 75 patients admitted to the same hospital during the same period of time who did not require critical care, aged under 75 years and with a Charlson comorbidity index equal to or less than 6 (non-critical group [nCC]) as a control group. Parameters from the nCC were compared with those from the CC.

Exclusion criteria were patients younger than 18 or older than 76, patients with a Charlson comorbidity index greater than 6, and patients in whom essential laboratory results were missing.

ICU admission criteria were: severe refractory respiratory failure secondary to COVID-19 pneumonia, with or without respiratory distress¹⁵, and the need for intubation and mechanical ventilation. Patients were only admitted to the ICU after weighing up the benefits of admission against their underlying comorbidities and frailty.

The study was approved by the Research Ethics Committee of the Hospital Clínico de Salamanca (PI 2020 05 487). The Ethics Committee waived the requirement for informed consent.

Data collection

All study data were collected from the medical records of patients in each group, and included clinical and anthropometric variables and laboratory results on arrival at the hospital emergency unit, prior to admission. We recorded patient-reported symptoms, onset of symptoms, date of hospital admission, date of admission to the critical care unit, and the treatment received. The Sequential Organ Failure Assessment (SOFA) score on arrival at the hospital was calculated to evaluate the patient's severity¹⁶. All data were reviewed by 2 physicians (PAP and ESB), and discrepancies were resolved by a third investigator (LMVR).

CRP and ferritin were chosen as biomarkers of the activation of different inflammatory pathways that could be associated with worsening clinical status^{10,11}. Four inflammatory profiles were created on the basis of blood test results.

Laboratory procedures

All patients underwent a SARS-CoV-2 rRT-PCR (real-time reverse transcriptase polymerase chain reaction) diagnostic test on admission using a nasopharyngeal swab. Blood tests included complete blood count, coagulation profile, serum biochemical tests (including kidney and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), CRP, interleukin-6 (IL-6), serum ferritin, and procalcitonin. Chest X-rays and computed tomography (CT) scans were performed on all patients if required during their stay.

Definitions

Fever was defined as an axillary temperature of at least 38°C. COVID-19 pneumonia was described as respiratory

symptoms (fever, dry cough, dyspnoea, etc.) plus infiltrates on the chest image²³. Acute respiratory distress syndrome (ARDS) was defined according to the internal WHO guidelines for the new coronavirus¹⁵. Hypoxaemia was defined as a partial pressure of oxygen (PaO₂)/inspired fraction of oxygen (FiO₂) ratio of less than 300 mmHg¹⁷, or an SpO₂/FiO₂ ratio of less than 220^{18,19}. Severe hypoxaemia was defined as PaO₂/FiO₂ less than 150 mmHg²⁰. Severe refractory respiratory failure was defined as failure (increased work of breathing or hypoxaemia) of standard oxygen therapy even after administration of O₂ through a non-rebreather face mask (flow rates 10-15 l/min and FiO₂ of 0.60-0.95)¹⁵.

Statistical analysis

Data were summarised using descriptive statistics. Missing data were not imputed. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Quantitative variables are expressed as mean and standard deviation or median and interquartile range (IQR: 25–75), and qualitative variables are expressed as percentages and whole numbers. Quantitative variables were compared using non-parametric tests when the distribution was not normal (Mann-Whitney U test) and parametric when it was normal (Student's t test). Qualitative variables were compared using the χ^2 or Fisher's exact tests.

We calculated the area under the curve (AUC-ROC) of the biomarkers with a p of <0.05 between the two groups in the univariate analysis. Of these, we selected only the 4 parameters with the best AUC in order to include the fewest possible number of covariates for the sample size²¹. The parameters chosen were used as covariates in a multivariate model to predict the primary outcome. We excluded variables from the multivariate analysis when the differences between groups were not significant, when the number of events was too small to calculate the odds ratios, and when the variable was co-linear with another variable.

To differentiate the groups, we also calculated the cut-off points for the selected variables by calculating their sensitivity and specificity and determining the best Youden index. We then used a forward stepwise approach (logistic regression) to create a model for the selected biomarkers. Only those with a p-value < 0.05 were included in the model, and those with a p value < 0.10 remained in the model, which was developed using simulated replicated data sets, calculating a mean difference in the AUC-ROC between these models and the best biomarkers, with a 95% CI. The DeLong test was used for this purpose. The Hosmer-Lemeshow multiple regression test was used to calibrate the model. To validate the generalizability of the critical risk scale we used data from a hospital (Hospital Universitario de León) that were not included in the development cohort. The 97 patients in this validation cohort had to fulfil the same inclusion criteria as the patients in the development cohort.

Finally, we obtained the best Youden index cut-off points (CPm) for ferritin and CRP from the ROC curves of these variables by calculating the sensitivity and specificity of these points. We used these data to define 4 inflammatory profiles based on lab results: profile 1 (if CRP > CPm and ferritin > CPm), profile 2 (if CRP > CPm and ferritin < CPm), profile 3 (if CRP < CPm and ferritin > CPm), and profile 4 (if

CRP < C_{Pm} and ferritin < C_{Pm}), which were then studied in the two groups. The level of significance was established at $p < 0.05$.

Statistical analysis was performed on SPSS 21[®] and Stata 15[®].

Results

Between 15 March and 15 April, 150 patients were included in this study: 75 patients who required admission to the ICU and formed the group of critical patients (CC) and 75 patients who did not, and were included in the control group (nCC). All CC patients were intubated and connected to mechanical ventilation. Four patients were excluded from this group due to missing data, so the final sample consisted of 146 patients.

The baseline characteristics and reasons for admission to the ICU are shown in Table 1. Mean age was 66 years (IQR: 57.75–71); 68% of all patients were male (60% in the non-critical group [nCC] vs 76% in the CC group ($p < 0.05$)). The most common underlying comorbidities were high blood pressure (62 [42.5%]), followed by obesity (46 [31.5%]), diabetes (31 [21.1%]), and heart disease (27 [18.5%]). Our study groups were evenly matched in terms of comorbidities.

Regarding symptoms and signs at the time of hospital admission, fever (119 [85%] patients), cough (86 [59%]) and dyspnoea (59 [40.4%]) were the most commonly reported. There were no significant differences between groups in terms of symptoms.

The mean time from onset of symptoms to hospital admission was 7 days (3–9) in both critical and non-critical patients. The time from disease onset to start of antiviral treatment was 8 days (7–11) in both groups. In the CC group, the mean time from onset of symptoms to admission to the ICU was 9 (7–14) days.

The in-hospital mortality rate was 27.4% in both groups, being significantly higher in the CC (40.8%) compared to the nCC (14.7%) group.

The different treatments administered to patients during their hospitalization are shown in Table 1. Although we observed a trend towards more hydroxychloroquine and azithromycin administration in the CC group ($p = 0.05$), more significant differences were observed in terms of treatment with high-dose heparin, IL-6 receptor inhibitors and corticosteroids, which were administered in 43%, 69% and 77.1% of patients in the CC group compared to 13.3% ($p = 0.000$), 50.7% ($p = 0.024$) and 40% ($p = 0.000$) patients in the nCC group, respectively.

Table 2 shows the results of the haemogram, coagulation and biochemical tests performed at the time of hospital admission, including pro-inflammatory markers. In the blood count, neutropaenia and lymphocytopaenia was more frequently observed in the group of patients who required admission to critical care units. Regarding the biochemical tests, higher baseline levels of creatinine, creatine kinase and lactate dehydrogenase were found in the CC group. Patients who required admission to the ICU also had higher baseline levels of fibrinogen, IL-6, CRP, procalcitonin, and ferritin as pro-inflammatory markers. Finally, the SaO₂/FiO₂ ratio was significantly lower in the CC vs the nCC group. It is interesting to note that patients requiring admission to the

ICU presented a considerably higher SOFA score on admission (Table 1). The SOFA score was calculated from 6 different organ system scores, In both groups, particularly in the CC group, the most important scores were obtained from the respiratory item (Tables 1 and 3).

Table 4 shows the AUCs for the parameters with significant differences between the nCC and CC groups and the cut-off points of the parameters that maintained their statistical significance in the logistic regression analysis. These variables were SOFA scale ≥ 2 (70% sensitivity and 76% specificity) and CRP ≥ 9.1 (75% sensitivity and 53% specificity). We also observed that the combined SOFA score and CRP level gave a sensitivity and specificity of 77%, which was significantly higher than the ROC curves for the SOFA score as an isolated variable. The AUC observed here (0.8) suggests that the SOFA score and CRP taken together at the time of hospital admission has a high predictive value.

In our multivariate logistic regression model, a high SOFA score gave an odds ratio of 1,968 for the need for admission to the ICU, and a high CRP value during admission was associated with an odds ratio of 1,052 for the need for ICU admission (Table 5). The presence of high levels of procalcitonin was also associated with an odds ratio of 1.152 for the need for critical care, although it was finally eliminated due to low specificity in the AUC.

The validation cohort included 97 patients with a mean age of 65 years (57–70), of which 71 (73%) were male and 96 (96%) had a Charlson index ≤ 4 . The SOFA variables collected for the validation cohort are shown in Table 3. The accuracy of the SOFA score was similar in both the validation and development cohorts, with an AUC of 0.89 in the validation cohort (95% CI: 0.82–0.95), a sensitivity of 86%, and a specificity of 72% ($p = 0.236$ compared to the development cohort).

Table 6 shows the distribution of patients in the nCC and CC groups according to their inflammatory profiles on arrival at the hospital. It is interesting to note that 67.7% of patients with inflammatory profile 1 (CRP > 9.1 mg/dl and ferritin > 969 ng/mL) during admission required critical care, while only 16.1% of those admitted with inflammatory profile 4 (CRP < 9.1 mg/dl and ferritin < 969 ng/mL) required critical care.

Discussion

We developed and validated a clinical risk scale to predict the progression of critical illness among patients hospitalized for COVID-19. The model performed well, showing a precision of 0.8 based on the AUC of both the development and validation cohorts.

The results of this retrospective study show that the presence of CRP levels ≥ 9.1 mg/dl and a SOFA score ≥ 2 in COVID-19 + patients at the time of hospital admission are independent predictors, with a sensitivity and specificity of 77%, of the need for admission to the ICU. This is the first time the combination of both these markers has been used to predict admission to intensive care in COVID-19 patients.

The association of the SOFA score with severity in COVID-19 patients has already been reported in other studies^{5,6}. However, the score of 2 observed in our series gave an acceptable AUC of 0.78 (0.70–0.86), which is in fact the cut-

Table 1 Baseline characteristics and COVID-19 parameters during admission.

	Total (n = 146)	Non-critical (nCC) (n = 75)	Critical (CC) (n = 71)	p
<i>Mean Age (± standard deviation)</i>	66.00 (57.75–71)	61.89 (55.25–70)	65.11 (60–72)	0.162
<i>Men, n (%)</i>	99 (67.8)	45 (60)	54 (76)	0.038
<i>Charlson index ≤ 4, n (%)</i>	141 (96.6)	74 (99)	66 (93)	0.105
<i>Underlying comorbidity, n (%)</i>				
High blood pressure	62 (42.5)	30 (40)	32 (45)	0.223
ACE/ARB inhibitor therapy	48 (32.9)	21 (28)	27 (38)	0.536
Obesity	46 (31.5)	22 (29.3)	24 (33.8)	0.197
Diabetes	31 (21.2)	14 (18.7)	17 (23.9)	0.436
History of thrombotic disease	9 (6.1)	5 (6.7)	4 (5.6)	0.346
Heart disease	27 (18.5)	15 (20)	12 (16.9)	0.674
Immunosuppression	13 (8.9)	7 (9.3)	6 (8.5)	0.852
Kidney failure	11 (7.5)	5 (6.7)	6 (8.5)	0.683
Smoking	10 (6.8)	4 (5.3)	6 (8.5)	0.525
COPD	10 (6.8)	5 (6.7)	5 (7)	0.928
Asthma	8 (5.5)	5 (6.7)	3 (4.3)	0.060
OSA	7 (4.8)	1 (1.3)	6 (8.5)	0.720
Active cancer	3 (2.1)	2 (2.7)	1 (1.4)	1.000
Others	13 (8.9)	7 (9.3)	6 (8.5)	0.861
<i>SOFA, median (IQR)</i>	2 (2–4)	1 (0–2)	3 (1–4)	0.000
Respiratory SOFA	1 (0–3)	1 (0–2)	2 (0–3)	0.000
Renal SOFA	0 (0–1)	0 (0–0)	0 (0–1)	0.123
Coagulatory SOFA	0 (0–1)	0 (0–1)	0 (0–1)	0.122
Cardiovascular SOFA	0 (0–0)	0 (0–0)	0 (0–1)	0.345
Liver SOFA	0 (0–0)	0 (0–0)	0 (0–0)	0.053
Neurological SOFA	0 (0–0)	0 (0–0)	0 (0–0)	0.432
<i>Non-survivors, n (%)</i>	40 (27.4)	11 (14.7)	29 (40.8)	0.001
<i>Signs and symptoms during admission, n (%)</i>				
Fever	119 (85.1)	59 (79.7)	60 (84.5)	0.364
Cough	86 (58.9)	39 (52)	47 (66.2)	0.081
Dyspnoea	59 (40.4)	31 (41.9)	28 (39.4)	0.815
Muscle pain	22 (15.1)	11 (14.7)	11 (15.5)	0.889
Diarrhoea	19 (13.1)	9 (12.0)	10 (14.1)	0.708
Asthenia	11 (7.53)	9 (12.2)	2 (2.8)	0.051
Neurological symptoms	8 (5.47)	5 (6.7)	3 (4.2)	0.314
Sore throat	3 (2.05)	1 (1.40)	2 (2.8)	1.000
Syncope	3 (2.05)	1 (1.40)	2 (2.8)	1.000
<i>Times, median (IQR)</i>				
Time from disease onset to hospitalization (days)	7 (3–9)	7 (3–10)	6 (3–9)	0.890
Time from disease onset to start of antiviral therapy (days)	8 (7–11)	7 (3–10)	7 (5–10)	0.412
Time from disease onset to start of hydroxychloroquine therapy (days)	7 (4–10)	7 (3–10)	7 (4–10)	0.479
Time from disease onset to start of interleukin-6 receptor blocker therapy (days)	8 (7–11)	9 (7–11)	8 (6–10)	0.148
Time from disease onset to intensive care admission (days)	NA	NA	9 (7–14)	NA
Time from hospital admission to intensive care admission (days)	NA	NA	3 (1–5)	NA
<i>Therapy during hospitalization</i>				
No heparin, n (%)	11 (7.53)	11 (14.6)	0	NA
Low-dose heparin, n (%)	111 (76.6)	54 (72.0)	57 (81.4)	0.181
High-dose heparin, n (%)	40 (28)	10 (13.3)	30 (43)	0.000
			3 (4.22) ^a	0.639

Table 1 (Continued)

	Total (n = 146)	Non-critical (nCC) (n = 75)	Critical (CC) (n = 71)	p
Azithromycin, n %	120 (82.2)	57 (76.0)	63 (88.7)	0.054
Interferon, n %	12 (8.2)	5 (6.7)	7 (9.9)	0.614
Hydroxychloroquine, n %	141 (96.6)	70 (93.4)	71 (100)	0.059
Lopinavir/ritonavir, (%)	137 (93.8)	68 (90.6)	69 (97.2)	0.102
Interleukin-6 receptor blockers, n (%)	87 (48.63)	38 (50.7)	49 (69.01)	0.024
			33 (46.5) ^a	0.612
Interleukin-1 receptor blockers, n (%)	3 (2.1)	1 (1.3)	2 (2.8)	NA
Steroids, n %	84 (59.7)	30 (40)	54 (77.1)	0.000
			23 (32.4) ^a	0.339

COPD: chronic obstructive pulmonary disease; NA: not applicable; OSA: obstructive sleep apnoea; SOFA: sequential organ failure assessment.

^a Treatment prior to transfer to the ICU.

Table 2 Laboratory parameters of COVID-19 patients during hospital admission according to ultimate destination.

	Total (n = 146)	Non-critical (n = 75)	Critical (n = 71)	p
Creatinine (mg/dl), median (IQR)	1.03 (0.81–1.22)	0.98 (0.72–1.18)	1.12 (0.92–1.31)	0.015
Bilirubin (mg/dl), median (IQR)	0.56 (0.39–0.72)	0.52 (0.34–0.67)	0.57 (0.39–0.76)	0.105
Creatine kinase (IU/l), median (IQR)	108 (56.25–192)	87 (52.5–168.5)	124.5 (56–306.25)	0.047
LDH (IU/l), median (IQR)	358 (286–458)	299 (239–365)	481 (365–615)	0.001
Bilirubin (g/dl), median (IQR)	3.8 (3.40–4.05)	3.8 (3.4–4.1)	3.7 (3.4–4)	0.069
TP (%), median (IQR)	86 (78–96)	86 (78.0–97.5)	86.0 (76.0–94.5)	0.645
TTPA (S), median (IQR)	33.6 (30.8–36.9)	33.5 (31.1–36.7)	33.7 (30.3–37.2)	0.380
INR, median (IQR)	1.10 (1.03–1.19)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.799
Fibrinogen (mg/dl), median (IQR)	619 (482–796)	588 (452–744)	676 (538–832)	0.016
D-dimer ($\mu\text{g}/\text{mL}$), median (IQR)	0.7 (0.4–1.10)	0.7 (0.40–1.0)	0.7 (0.4–1.3)	0.152
Platelets ($\times 10^9/\text{l}$), median (IQR)	177 (143–227)	180 (135–237)	173 (148–226)	0.906
Neutrophils ($\times 10^9/\text{l}$), median (IQR)	5.17 (3.62–8.64)	4.26 (3.14–6.26)	6.13 (3.90–9.86)	0.007
Lymphocytes ($\times 10^9/\text{l}$), median (IQR)	0.795 (0.65–1.11)	0.94 (0.71–1.22)	0.72 (0.62–1.00)	0.009
Haemoglobin (g/dl), median (IQR)	14.20 (13–15.4)	14.15 (13–15.33)	14.2 (12.95–15.50)	0.596
CRP (mg/dl) median (IQR)	10.6 (5.6–20.26)	8.03 (4.01–14.9)	13.49 (8.91–28.98)	0.000
Procalcitonin (ng/mL), median (IQR)	0.13 (0.08–0.38)	0.10 (0.06–0.28)	0.25 (0.12–0.47)	0.000
IL-6 (pg/mL), median (IQR)	42.2 (22.1–111.65)	31.05 (9.90–42.35)	56.55 (21.88–188)	0.001
Ferritin (ng/mL), median (IQR)	1,118 (567–2052)	927 (398–1398)	1,416 (805–2606)	0.007
Troponin (pg/mL), median (IQR)	12.85 (10.69–18.05)	15.53 (10.25–17.23)	12.85 (9.29–123.08)	0.945
SaO ₂ /FiO ₂ , median (IQR)	424 (346–448)	433 (419–452)	361 (180–428)	0.000

APTT: activated partial thromboplastin time; CRP: C-reactive protein; LDH: lactate dehydrogenase; IL-6: interleukin-6; IQR: interquartile range; PT: prothrombin time.

Normal range: TP (11–13.5 s); APTT (27–40 s); Fibrinogen (130–400 mg/dl); D-dimer ($<0.5 \mu\text{g}/\text{mL}$); Platelet count ($150 \times 10^9/\text{l}$ – $400 \times 10^9/\text{l}$); Lymphocyte count (1.2 – $3.5 \times 10^9/\text{l}$); Neutrophil count (1.4 – $6.5 \times 10^9/\text{l}$); LDH (135–225 IU/l); CK (34–145 IU/l); PCR ($<0.5 \text{ mg}/\text{mL}$); Creatinine (0.5–0.9 mg/mL); Bilirubin (0.15–1.2 mg/ml); Albumin (3.5–5.2 g/dl); Procalcitonin (0–0.5 ng/mL); IK6 (0–3.4 pg/mL); Ferritin (15–150 ng/mL); Troponin (0–210 pg/mL).

off point for distinguishing between septic and non-septic patients¹⁶. Although this applies to bacterial infections, viral infections can lead to sepsis, and nearly 40% of adults with community-acquired pneumonia due to viral infection develop sepsis²².

In our series, the SOFA score was shown to be a predictor of the need for critical care after correcting for the remaining main covariates, such as CRP, procalcitonin, and sex. Tables 1 and 3 show the importance of the respiratory item in the SOFA score at the time of admission, as expected.

Regarding CRP, other authors have reported that high values are related to prognosis and severity in COVID-19^{23,24}.

In our series, the role of CRP as a predictor of the need for critical care maintained its significance in the univariate analysis, and the cut-off point of 9 mg/dl proved to be the most sensitive and specific factor to discriminate between patients who will require critical care versus those who will not. The role of CRP as a predictive factor was maintained in the multivariate analysis. As CRP is mainly synthesised in response to pro-inflammatory cytokines¹⁰, particularly IL-6 and to a lesser degree IL-1, and tumour necrosis factor alpha (TNF- α), it should be determined at the time of admission, since it is more accessible than the other proxies of pro-inflammatory cytokine.

Table 3 Laboratory characteristics of patients in the validation cohort, sensitivity and specificity, and cut-off points.

	Total (n = 97)	Non-critical (n = 45)	Critical (n = 52)	Sensitivity (S); Specificity (Sp)
CRP (mg/dl) median (IQR)	10.9 (6.5–29.8)	7.4 (1.8–11.8)	16.8 (9.5–25.6)	77% S; 63% Sp
SOFA, median (IQR)	3 (2–4)	2 (1–3)	4 (3–4)	86% S; 69% Sp
Respiratory SOFA	2 (1–3)	1 (0–2)	3 (2–3)	
Renal SOFA	0 (0–0)	0 (0–0)	0 (0–0)	
Coagulatory SOFA	0 (0–0)	0 (0–0)	0 (0–1)	
Cardiovascular SOFA	0 (0–0)	0 (0–0)	0 (0–1)	
Liver SOFA	0 (0–0)	0 (0–0)	0 (0–0)	
Neurological SOFA	0 (0–0)	0 (0–0)	0 (0–0)	

CRP: C-reactive protein; SOFA: sequential organ failure assessment.
 Multiple regression: OR SOFA: 2.46 (1.54–3.95); OR CRP: 1.08 (1.01–1.16).
 Hosmer-Lemeshow test: χ^2 4.71; 8 gl; p = 0.785.

Table 4 AUC-ROC and cut-off point, sensitivity and specificity of COVID-19 parameters to predict the likelihood of critical care at the time of admission.

	AUC-ROC	Cut-off point	Sensitivity (%)	Specificity (%)
SOFA	0.78 (0.70–0.86)	≥ 2	70	76
Procalcitonin	0.74 (0.66–0.83)	≥ 0.1 ng/mL	88	52
CRP	0.69 (0.61–0.78)	≥ 9.1 mg/dl	75	53
Ferritin ^a	0.68 (0.56–0.83)	≥ 969 ng/mL	74	56
LDH	0.67 (0.58–0.76)	NA		
Neutrophils	0.64 (0.56–0.73)	NA		
Lymphocytes	0.63 (0.54–0.73)	NA		
Glucose	0.63 (0.54–0.72)	NA		
Fibrinogen	0.63 (0.53–0.72)	NA		
CK	0.62 (0.52–0.71)	NA		
IL-6 ^a	NA	NA		
Combination (SOFA-CRP)	0.83 (0.76–0.90)	≥ 0.43 ^b	77	77

CK: creatine kinase; CRP: C-reactive protein; IL-6: interleukin-6; NA: not applicable; SOFA: sequential organ failure assessment.

^a Ferritin and IL-6 are excluded from the model due to the low number of subjects.

^b Cut-off point for combination SOFA-CRP = $1 + 1/e^{-2,186 + 0.68 \times \text{SOFA score} + 0.05 \times \text{CRP value}}$.

Table 5 Multiple regression using the 4 covariates of interest.

	B coefficient	OR (95% CI)
SOFA	0.68	1.968 (1.389–2.590)
CRP	0.05	1.052 (1.009–1.101)
Procalcitonin	0.14	1.152 (0.770–1.979)
Sex	-0.21	0.806 (0.309–1.993)
Constant	-2.19	

In our series, a combination of CRP and SOFA yielded an AUC of 0.83 (0.76–0.90). This is excellent for predicting the need for intensive care during admission, and to our knowledge had not been previously reported. It is also plausible on a biological level, since, as in other infectious processes²⁵, the combination of one of the main markers of inflammation (CRP) with a validated organ failure scale (SOFA) can provide a more accurate diagnosis/prognosis in patients with COVID-19.

Another important finding in this study has been that almost 70% of patients admitted with CRP levels of over 9.1 mg/dl and ferritin of over 969 ng/mL required critical

care. This suggests that these parameters can also accurately predict prognosis. An inflammatory profile consisting of CRP < 9.1 mg/dl and ferritin < 969 ng/mL would help identify patients that are unlikely to require critical care. In fact, only 16% of patients in our series with this profile required admission to the ICU.

As mentioned previously, CRP is involved in the IL-6 pathway. IL-1 and IL-6 have been shown to trigger acute activation of endothelial cells²⁴ causing high levels of these and other cytokines in critically ill patients²⁶. Ferritin is also involved in the IL-1 pathway^{10,11}, therefore, the combination of CRP and ferritin may constitute an inflammatory pattern with prognostic potential.

Procalcitonin has been associated with prognosis in patients with an inflammatory response similar to that found in our series²⁷. However, its role as a predictor of critical care was not maintained in the multivariate analysis, perhaps due to its poor diagnostic performance in viral infections²⁸.

Sex has been described in other series as a prognostic factor^{8,9} of overall mortality. However, in our study, male sex did not predict an increased risk of requiring critical care. The same was true of time to hospital admission or

Table 6 Inflammatory profile in COVID-19 patients during admission, according to their ultimate destination.

	Total (n = 65)	Non-critical (n = 34)	Critical (n = 31)	p
Profile 1, n (%) (CRP \geq 9.1 mg/dl and ferritin \geq 969 ng/mL)	30 (46.2)	9 (26.5)	21 (67.7)	0.007
Profile 2, n (%) (CRP \geq 9.1 mg/dl and ferritin < 969 ng/mL)	9 (13.8)	6 (17.6)	3 (9.7)	1.000
Profile 3, n (%) (CRP < 9.1 mg/dl and ferritin \geq 969 ng/mL)	8 (12.3)	6 (17.6)	2 (6.5)	0.563
Profile 4, n (%) (CRP < 9.1 mg/dl and ferritin < 969 ng/mL)	18 (27.7)	13 (38.2)	5 (16.1)	0.016

Calculated in patients with ferritin and CRP lab results.

to start of treatment. Comorbidity derived from underlying diseases upon arrival at the hospital was similar in both groups, except for asthma, which has been identified in other studies²⁹. Regarding treatment, the group of critically ill patients received more than expected amount of high-dose heparin, interleukin receptor inhibitors, and corticosteroids, due to their severity.

Other authors have suggested that LDH, CK, and white blood cells can be prognostic factors^{3,5,7,30}, particularly of viral load (LDH and CK)³⁰. In our case, they were not included in the multivariate analysis because they presented a lower AUC than that required for diagnosis.

Our study has certain limitations due to its retrospective nature, and some laboratory data were missing in some patients. We used a small sample to construct the risk scale and a relatively small sample for validation purposes. Despite this small sample size, the inclusion of randomized adult COVID-19 patients is representative of the number of cases treated in critical care units.

Finally, in general and as expected, the in-hospital mortality rate in patients who required admission to the ICU was more than double that of patients not requiring critical care. The mortality rate reported here is consistent with that published in other series³, and shows that it is crucial to identify this group of patients at the time of admission. As patients with a SOFA score > 2 and high levels of CRP appear more likely to require critical care, additional therapeutic actions could be taken to reduce the need for such care and thus reduce the in-hospital mortality rate. However, further studies and prospective trials are needed to support this finding.

Conclusion

COVID-19 patients with a SOFA score \geq 2 and CRP \geq 9.1 mg/mL could constitute a population that is most likely to require critical care.

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Authorship

LMVR designed the study. Data were collected by ESB, DEM, PAP and RG. Data analysis was performed by LMVR. LMVR and JRGP wrote the manuscript with input from all authors. MVSH critically reviewed the manuscript for important intel-

lectual content. All authors approved the final version of the study.

Conflict of interests

None.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.redar.2020.11.014>.

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