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Letter to the Editor

A quick prediction tool for unfavourable outcome in COVID-19 inpatients: Development and internal validation

Dear editor,

As COVID-19 pandemic continues to escalate, hospitals around the world confront with the need to attend an increasing number of patients. Therefore, we read with much interest the recent study published in the Journal of Infection by Galloway JB et al., reinforcing the importance of stratifying patients to ease their management and their incorporation to potential clinical trials[1]. For this purpose, these authors developed a valuable and complex risk score based on twelve parameters, including, among others, age, gender, diabetes mellitus, hypertension, and chronic lung disease. Since knowing the risk of clinical deterioration can assist medical decisions about appropriate level of care, predictive models for COVID-19 are becoming notably frequent. However, many of them are notably biased, non-validated, or present a construction lacking in clarity[2,3]. Moreover, they often conclude that male older patients with comorbidities are more likely to experience unfavourable outcomes[4,5], even when such determinants are already well-known predictors of worse result in community-acquired pneumonia[6]. Although the medical assessment of patients must always address demographics and underlying comorbidities, it is known that the evaluation of disease severity and prognosis should not only depend on the above-mentioned risk markers.

Our aim was to help clinicians rapidly identify which patients, attended for the first time in an emergency room and regardless of their age, sex, or comorbid conditions, are more likely to be transferred to the intensive care unit (ICU) or to die, and are therefore candidates for a close monitoring and for the administration of the best available therapy. Thus, we focused on the simplest and readily available hemodynamic and laboratory features to build a quick prognostic equation that, based on five independent predictors, was able to estimate the probability of ICU admission or death among adult COVID-19 inpatients.

Briefly, we conducted a prospective cohort study in Virgen del Rocío University Hospital, a Spanish tertiary-care-teaching centre, where 244 consecutive patients, diagnosed of COVID-19, were enrolled from February 21 to April 8, 2020, and followed-up for 28 days. Data were recorded at the emergency room or upon hospital admission. Primary endpoints were favourable (disease improvement, full recovery and discharge, and/or maintenance of non-critical status) and unfavourable (death and/or ICU admission) clinical outcomes. The study protocol was approved by the Ethics Committee (C.I. 0771-N-20) and complied the Declaration of Helsinki. Further information on study design, statistical approach, and internal validation is provided in the Supplementary materials text, Supplementary Table S1, and Supplementary Table S2.

Patients' characteristics are shown in Table 1. One-hundred-thirty-two (54.1%) were male and median age was 64 (IQR 55–76) years. Older, institutionalized, solid organ transplant recipients, and hypertensive patients were more likely to develop an unfavourable clinical outcome. Dyspnoea, diastolic hypotension, tachycardia, tachypnoea, low peripheral capillary oxygen saturation (SpO2), chest bilateral infiltrates, high qSOFA and CURB-65 scores were also closely linked to a worse prognosis. Leucocytosis, neutrophilia, lymphocytopenia, thrombocytopenia, and high values of neutrophil-to-lymphocyte ratio, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), d-dimer, creatinine, and aspartate aminotransferase were more frequent in the unfavourable outcome group. Forty-three (17.6%) patients were admitted to the ICU. The occurrence of ICU transfer by age-group was: $<$50 years, $n=6$ (15.4%); 50–64 years, $n=17$ (20.0%); $\geq$65 years, $n=20$ (16.7%). Overall mortality rate (12.7%) and short-term mortality distribution are described in Supplementary Figure S1.

Twenty-three categorical variables were identified as potential independent predictors of unfavourable outcome in univariable logistic regression analysis (Supplementary Table S3). We found significant differences between the survival functions of SpO2 $<$95% (log-rank, $p<0.003$) and CRP $\geq$100 mg/L ($p=0.015$), and the adjusted Cox regression analysis showed that hypoxemic patients and those presenting high CRP were indeed more likely to die earlier (Supplementary Figure S2). The prognosis model was composed of five predictors, demonstrated as independent risk factors in the adjusted multivariable logistic regression analysis: SpO2 $<$95%, neutrophil count $>7.5\times10^9$ per L, platelet count $<130\times10^9$ per L, LDH $\geq$300 UI/L, and CRP $\geq$100 mg/L (Supplementary Figure S3). A final model description, its overall apparent performance, and the explanation on how to implement it are presented in Table 2.

Unlike the rest of prognosis models published[1,3,7–9], that included already well-established and globally accepted clinical predictors of severity[6], we opted for incorporating exclusively the explanatory variables that were directly related to the pathogenesis of COVID-19. In this respect, the biological plausibility of hypoxemia, thrombocytopenia, neutrophilia, and high levels of LDH and CRP, coupled with their important role in disease progression, make our selected variables of great interest for further research on SARS-CoV-2 damaging mechanisms and therapeutic targets. Hypoxemia and high LDH, expression of tissue damage, contributed to build Ji et al., Liang et al. and Galloway et al. predictive tools[1,7,9]. Gong et al. and Galloway et al., like us, included CRP and neutrophil count as inflammation markers in their model, but in conjunction with other not as easily accessible predictors, like albumin[1,3]. The low platelet count, despite its likely interlinkage with thrombosis in the pathogenesis of COVID-19, has not yet been thor-

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Table 1
Characteristics of the cohort *versus* clinical outcome.

	Total ($n=244$)	Clinical outcome		OR/MD (95% CI)	p value
		Favourable ($n=179$)	Unfavourable ($n=65$)		
Demographics					
Age, years	64 (55–76)	62 (16)	70 (14)	8 (4–12)	<0.001
Age group ≥65 years	120 (49.2%)	78 (43.6%)	42 (64.6%)	2.37 (1.31–4.26)	0.004
Male sex	132 (54.1%)	93 (52.0%)	39 (60.0%)	1.39 (0.78–2.47)	0.265
Underlying conditions					
Smoking history	18 (7.4%)	13 (7.3%)	5 (7.7%)	1.06 (0.36–3.11)	1.000
Drinking history	8 (3.3%)	4 (2.2%)	4 (6.2%)	2.87 (0.70–11.82)	0.266
Diabetes mellitus	46 (18.9%)	32 (17.9%)	14 (21.5%)	1.26 (0.62–2.55)	0.518
Hypertension	122 (50.0%)	82 (45.8%)	40 (61.5%)	1.89 (1.06–3.38)	0.030
Malignancy	19 (7.8%)	11 (6.1%)	8 (12.3%)	2.14 (0.82–5.59)	0.112
Cerebrovascular disease	11 (4.5%)	7 (3.9%)	4 (6.2%)	1.61 (0.46–5.70)	0.691
Dementia	20 (8.2%)	14 (7.8%)	6 (9.2%)	1.20 (0.44–3.26)	0.723
COPD	10 (4.1%)	6 (3.4%)	4 (6.2%)	1.89 (0.52–6.93)	0.541
OSA	3 (1.2%)	3 (1.7%)	0	..	0.694
Asthma	10 (4.1%)	10 (5.6%)	0	..	0.114
Chronic cardiopathy	44 (18.0%)	29 (16.2%)	15 (23.1%)	1.55 (0.77–3.13)	0.217
Chronic renal impairment	18 (7.4%)	14 (7.8%)	4 (6.2%)	0.77 (0.25–2.44)	0.870
Chronic liver impairment	9 (3.7%)	6 (3.4%)	3 (4.6%)	1.40 (0.34–5.75)	0.937
Connective tissue disease	13 (5.3%)	9 (5.0%)	4 (6.2%)	1.24 (0.37–4.17)	0.981
SOT	5 (2.0%)	1 (0.6%)	4 (6.2%)	11.67 (1.28–106.46)	0.027
Residence in a socio-sanitary/geriatric centre	35 (14.3%)	19 (10.6%)	16 (24.6%)	2.75 (1.32–5.75)	0.006
Charlson Index ≥3	139 (57.0%)	92 (51.4%)	47 (72.3%)	2.47 (1.33–4.58)	0.004
Previous treatment					
ACEi	47 (19.3%)	35 (19.6%)	12 (18.5%)	0.93 (0.45–1.93)	0.848
Statins	40 (16.4%)	26 (14.5%)	14 (21.5%)	1.62 (0.78–3.33)	0.191
Immunosuppressive drugs	30 (12.3%)	21 (11.7%)	9 (13.8%)	1.21 (0.52–2.80)	0.675
Clinical symptoms at diagnosis					
Time from symptoms onset to hospital admission, days	7 (5–11)	8 (5–12)	7 (4–10)	2 (0–4)	0.051
Rhinorrhoea	15 (6.1%)	13 (7.3%)	2 (3.1%)	0.41 (0.09–1.85)	0.367
Odynophagia	17 (7.0%)	12 (6.7%)	5 (7.7%)	1.16 (0.39–3.43)	1.000
Cough	175 (71.7%)	132 (73.7%)	43 (66.2%)	0.70 (0.38–1.28)	0.245
Expectoration	25 (10.2%)	18 (10.1%)	7 (10.8%)	1.08 (0.43–2.72)	0.871
Pleuritic chest pain	12 (4.9%)	10 (5.6%)	2 (3.1%)	0.54 (0.11–2.52)	0.641
Dyspnoea	118 (48.4%)	78 (43.6%)	40 (61.5%)	2.07 (1.16–3.70)	0.013
Diarrhoea	41 (16.8%)	35 (19.6%)	6 (9.2%)	0.42 (0.17–1.05)	0.057
Vomits	17 (7.0%)	16 (8.9%)	1 (1.5%)	0.16 (0.02–1.23)	0.085
Arthromyalgia	54 (22.1%)	39 (21.8%)	15 (23.1%)	1.08 (0.55–2.12)	0.830
Weakness	62 (25.4%)	48 (26.8%)	14 (21.5%)	0.75 (0.38–1.48)	0.403
Headache	43 (17.6%)	30 (16.8%)	13 (20.0%)	1.24 (0.60–2.56)	0.557
Impaired consciousness	8 (3.3%)	4 (2.2%)	4 (6.2%)	2.87 (0.70–11.82)	0.266
Anosmia	26 (10.7%)	21 (11.7%)	5 (7.7%)	0.63 (0.23–1.74)	0.366
Dysgeusia	27 (11.1%)	23 (12.8%)	4 (6.2%)	0.45 (0.15–1.34)	0.141
Vital signs, exploration, and severity scores at diagnosis					
Temperature, °C	36.7 (36.0–37.7)	36.7 (36.0–37.7)	37.0 (1.2)	0.2 (−0.1–0.6)	0.211
Temperature >37.5 °C	72 (30.0%)	50 (28.4%)	22 (34.4%)	1.32 (0.72–2.43)	0.372
SBP <90 mmHg	9 (3.7%)	5 (2.8%)	4 (6.5%)	2.40 (0.62–9.24)	0.357
DBP <60 mmHg	25 (10.4%)	11 (6.1%)	14 (22.6%)	4.46 (1.90–10.45)	<0.001
HR >100 bpm	61 (25.3%)	38 (21.6%)	23 (35.4%)	1.99 (1.07–3.71)	0.029
RR >20 bpm	37 (15.6%)	14 (7.9%)	23 (38.3%)	7.24 (3.40–15.39)	<0.001
SpO2, %	95 (92–97)	96 (94–97)	90 (85–93)	7 (5–9)	<0.001
SpO2 <95%	114 (47.1%)	56 (31.6%)	58 (89.2%)	17.90 (7.68–41.71)	<0.001
Pathological respiratory exploration	153 (62.7%)	113 (63.1%)	40 (61.5%)	0.94 (0.52–1.68)	0.820
qSOFA ≥2	23 (9.4%)	12 (6.7%)	11 (16.9%)	2.84 (1.18–6.79)	0.016
CURB-65 ≥ 2	74 (30.3%)	38 (21.2%)	36 (55.4%)	4.61 (2.51–8.45)	<0.001
Chest x-ray findings					
Dominant interstitial pattern	145 (59.4%)	103 (57.5%)	42 (64.6%)	1.35 (0.75–2.43)	0.320
Dominant alveolar pattern	69 (28.3%)	49 (27.4%)	20 (30.8%)	1.18 (0.63–2.19)	0.603
Unilateral infiltrates	41 (16.8%)	36 (20.1%)	5 (7.7%)	0.33 (0.12–0.88)	0.022
Bilateral infiltrates	173 (70.9%)	116 (64.8%)	57 (87.7%)	3.87 (1.74–8.62)	0.001
Laboratory results					
WBC count, $x10^9$ per L	6.8 (4.9–9.1)	6.5 (4.8–8.5)	7.8 (5.0–11.7)	3.9 (0.1–7.7)	0.046
WBC count $>11.0\times10^9$ per L	34 (14.0%)	14 (7.9%)	20 (30.8%)	5.21 (2.44–11.12)	<0.001
Neutrophil count, $x10^9$ per L	5.0 (3.4–7.1)	4.6 (3.3–6.3)	6.7 (3.7–9.7)	0.2 (−10.3–10.7)	0.972
Neutrophil count $>7.5\times10^9$ per L	52 (21.5%)	25 (14.1%)	27 (41.5%)	4.32 (2.26–8.27)	<0.001
Lymphocyte count, $x10^9$ per L	1.1 (0.7–1.5)	1.1 (0.8–1.6)	0.8 (0.6–1.3)	3.1 (−1.1–7.3)	0.147
Lymphocyte count $<1.0\times10^9$ per L	111 (45.7%)	69 (38.8%)	42 (64.0%)	2.89 (1.60–5.21)	<0.001
NLR	4.4 (2.7–7.9)	3.7 (2.4–6.8)	6.5 (3.7–12.4)	11.3 (−9.6–32.3)	0.284
NLR >3.04	161 (66.5%)	108 (61.0%)	53 (81.5%)	2.82 (1.41–5.66)	0.003
Platelet count, $x10^9$ per L	201 (163–264)	200 (165–265)	201 (155–265)	6 (−18–31)	0.603
Platelet count $<130\times10^9$ per L	22 (9.1%)	12 (6.8%)	10 (15.4%)	2.49 (1.02–6.07)	0.040
CRP, mg/L	69 (32–149)	54 (23–112)	175 (68–256)	124 (56–193)	0.001
CRP ≥100 mg/L	89 (37.9%)	51 (29.5%)	38 (61.3%)	3.79 (2.07–6.95)	<0.001

(*continued on next page*)

Table 1 (*continued*)

Ferritin, ng/mL	521.0 (248.3–1158.7)	419.3 (227.4–977.6)	824.5 (405.7–1712.2)	356.7 (10.8–702.6)	0.043
Ferritin ≥1000 ng/mL	46 (30.5%)	24 (22.6%)	22 (48.9%)	3.27 (1.56–6.85)	0.001
D-dimer, ng/mL	790 (473–1650)	730 (460–1455)	1160 (678–2333)	3019 (−875–6912)	0.126
D-dimer ≥600 ng/mL	143 (64.7%)	98 (59.4%)	45 (80.4%)	2.80 (1.35–5.80)	0.005
LDH, UI/L	321 (244–424)	297 (234–377)	420 (321–516)	129 (73–186)	<0.001
LDH ≥300 UI/L	130 (58.0%)	81 (48.8%)	49 (84.5%)	5.71 (2.64–12.38)	<0.001
Creatinine >1.3 mg/dL	47 (21.5%)	28 (17.7%)	19 (31.1%)	2.10 (1.07–4.14)	0.030
AST, UI/L	30 (23–52)	27 (22–45)	44 (30–64)	25 (3–48)	0.028
AST >30 UI/L	104 (49.8%)	61 (40.7%)	43 (72.9%)	3.92 (2.03–7.59)	<0.001
ALT, UI/L	28 (18–46)	24 (18–47)	33 (22–46)	3 (−14–21)	0.691
ALT >40 UI/L	63 (30.1%)	43 (28.7%)	20 (22.9%)	1.28 (0.67–2.43)	0.458
Hospital stay					
ALOS, days	7 (3–13)	6 (3–9)	16 (6–29)	11 (7–15)	<0.001
LOS >30 days	21 (8.6%)	6 (3.4%)	15 (23.1%)	8.65 (3.19–23.46)	<0.001
Treatments administered					
Initial antiviral treatment					
None	20 (8.2%)	11 (6.1%)	9 (13.8%)	2.46 (0.97–6.23)	0.053
LPV/r monotherapy	7 (2.9%)	6 (3.4%)	1 (1.5%)	0.45 (0.05–3.82)	0.752
HCQ monotherapy	37 (15.2%)	34 (19.0%)	3 (4.6%)	0.21 (0.06–0.70)	0.006
LPV/r + HCQ	132 (54.1%)	106 (59.2%)	26 (40.0%)	0.46 (0.26–0.82)	0.008
LPV/r + HCQ + IFN-β	48 (19.7%)	22 (12.3%)	26 (40.0%)	4.76 (2.44–9.27)	<0.001
Time from symptoms onset to start of antiviral treatment, days	8 (6–12)	8 (6–12)	8 (6–11)	1 (−1–3)	0.553
Antiviral treatment added during hospitalization					
LPV/r	10 (4.1%)	9 (5.0%)	1 (1.5%)	0.30 (0.04–2.38)	0.395
IFN-β	15 (6.1%)	6 (3.4%)	9 (13.8%)	4.63 (1.58–13.59)	0.003
Remdesivir	2 (0.8%)	0	2 (3.1%)	..	0.120
Anti-inflammatory treatment added during hospitalization					
Tocilizumab	28 (11.5%)	0	28 (43.1%)	..	<0.001
Azithromycin	83 (34.0%)	43 (24.0%)	40 (61.5%)	5.06 (2.76–9.28)	<0.001
Steroid therapy	61 (25.0%)	32 (17.9%)	29 (44.6%)	3.70 (1.99–6.88)	<0.001
Oxygen support					
HFT in ward	61 (25.0%)	19 (10.6%)	42 (64.6%)	15.38 (7.67–30.85)	<0.001
NIMV in ward	20 (8.2%)	6 (3.4%)	14 (21.5%)	7.92 (2.89–21.65)	<0.001
IMV	28 (11.5%)	0	28 (43.1%)	..	<0.001
Complications					
ARDS	36 (14.8%)	4 (2.2%)	32 (49.2%)	42.42 (14.07–127.96)	<0.001
Multiorgan failure	2 (0.8%)	0	2 (3.1%)	..	0.120
Septic shock	5 (2.0%)	1 (0.6%)	4 (6.2%)	11.67 (1.28–106.46)	0.027
Acute kidney injury	5 (2.0%)	3 (1.7%)	2 (3.1%)	1.86 (0.30–11.41)	0.864

Data are n (%), median (IQR), mean (SD), or odds ratio/mean difference (95% CI), according to indication. p values (two-tailed) were calculated by χ^2-test, YatesCorrection for Continuity, Studentś *t*-test, or Welchś *t*-test, as appropriate. OR=odds ratio. MD=mean difference. CODP=chronic obstructive pulmonary disease. OSA=obstructive sleep apnoea. SOT=solid organ transplant. ACEi=angiotensin-converting-enzyme inhibitors. SBP=systolic blood pressure. DBP=diastolic blood pressure. HR=heart rate. RR=respiratory rate. SpO2=peripheral capillary oxygen saturation. WBC=white blood cell. NLR=neutrophil-to-lymphocyte ratio. CRP=C-reactive protein. LDH=lactate dehydrogenase. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ALOS=average length of stay. LOS=length of stay. LPV/r=lopinavir/ritonavir. HCQ=hydroxychloroquine. IFN-β=beta interferon. HFT=high flow therapy. NIMV=non-invasive mechanical ventilation. IMV=invasive mechanical ventilation. ARDS=acute respiratory distress syndrome. Data were missing for symptoms onset in one (0.4%) patient, for temperature in four (1.6%), for blood pressure in three (1.2%), HR in three (1.2%), RR in seven (2.9%), SpO2 in two (0.8%) WBC count in one (0.4%), neutrophil count in two (0.8%), lymphocyte count in one (0.4%), platelet count in three (1.2%), CRP in nine (3.7%), ferritin in 93 (38.1%), d-dimer in 23 (9.4%), LDH in 20 (8.2%), creatinine in 25 (10.2%), and for liver enzymes in 35 (14.3%) patients.

oughly explored. Zhao et al. discussed the tendency of these cells to decrease in critically ill patients[10]. Our study goes one step further and offers thrombocytopenia at the moment of hospital admission as a main predictor for short-term adverse clinical outcomes.

In conclusion, we derived and validated a prognostic model, including five common features obtained in the first patient's evaluation at the emergency room, with high sensitivity and specificity to discriminate individuals that might develop critical disease or die, from those with a favourable course. This model, besides the complete clinical evaluation of the patient by the physician, could be helpful for guiding prompt decision-making, improve the management of COVID-19 patients, alleviate insufficiency of medical resources, and reduce mortality.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Sonsoles Salto-Alejandre: Investigation, Writing - original draft, Writing - review & editing. **Cristina Roca-Oporto:** Data curation, Writing - review & editing. **Guillermo Martín-Gutiérrez:** Data curation, Writing - review & editing. **María Dolores Avilés:** Data curation, Writing - review & editing. **Carmen Gómez-González:** Data curation, Writing - review & editing. **María Dolores Navarro-Amuedo:** Data curation, Writing - review & editing. **Julia Praena-Segovia:** Data curation, Writing - review & editing. **José Molina:** Data curation, Writing - review & editing. **María Paniagua-García:** Data curation, Writing - review & editing. **Horacio García-Delgado:** Data curation, Writing - review & editing. **Antonio Domínguez-Petit:** Data curation, Writing - review & editing. **Jerónimo Pachón:** Conceptualization, Visualization, Investigation, Writing - original draft, Writing - review & editing. **José Miguel Cisneros:** Conceptualization, Visualization, Writing - review & editing.

Table 2
Final prognosis model description.

	B (SE)	W^2 (df)	OR (95% CI)	p value
SpO2 <95%	3.075 (0.539)	32.509 (1)	21.66 (7.52–62.33)	<0.001
Neutrophil count $>7.5\times10^9$ per L	1.324 (0.478)	7.674 (1)	3.76 (1.47–9.59)	0.006
Platelet count $<130\times10^9$ per L	1.492 (0.649)	5.280 (1)	4.45 (1.25–15.87)	0.022
LDH ≥300 UI/L	0.981 (0.491)	3.991 (1)	2.67 (1.02–6.98)	0.046
CRP ≥100 mg/L	0.916 (0.434)	4.466 (1)	2.50 (1.07–5.85)	0.035
Constant	−4.655 (0.656)	50.423 (1)	..	..

Variables in the final multivariable logistic regression model are accompanied by the beta coefficient (SE), Wald-statistic (df), adjusted odds ratio (95% CI), and two-tailed p value. Information concerning the constant is provided as beta coefficient (SE) and Wald-statistic (df). *B*=beta coefficient. SE=standard error. W^2=Wald-statistic. df=degrees of freedom. OR=odds ratio. SpO2=peripheral capillary oxygen saturation. LDH=lactate dehydrogenase. CRP=*C*-reactive protein.
The model was composed of five variables (therefore 13 events per variable) demonstrated as independent risk factors in the multivariable logistic regression analysis: SpO2 <95%, neutrophil count $>7.5\times10^9$ per L, platelet count $<130\times10^9$ per L, LDH ≥300 UI/L, and CRP ≥100 mg/L (Supplementary Figure S3). It reported an overall apparent performance of 82.9% (sensitivity 62.5%, specificity 90.1%, PPV 68.6%, NPV 87.4%). Its discrimination power (C-index) was expressed by an AUC-ROC of 0.891 (standard error 0.020, 95% CI 0.847–0.936; $p<0.001$) (Supplementary Figure S4). The variables included were explanatory, being −2LL=151.615 (χ^2 96.208, df 5; $p<0.001$), and contributed to giving the model an ability to explain roughly 53% of the variation of the outcome (Nagelkerke R^2 0.526). The model was a good fit to the dataset (Hosmer-Lemeshow χ^2 1.130, df 5; $p=0.951$), which could also be tested visually by the calibration plot (Supplementary Figure S5). After 100 iterations of bootstrapping, model optimism was estimated <0.01 (SD 0.02), indicating minimal overfitting to the data. The optimism-corrected performance was of 0.885. The final equation to estimate the probability (0 to 1) of unfavourable outcome was: Logit (logarithm of the odds) (pi) = −4.655 + 3.075 (SpO2 <95%) + 1.324 (neutrophil count $>7.5\times10^9$ per L) + 1.492 (platelet count $<130\times10^9$ per L) + 0.981 (LDH ≥300 UI/L) + 0.916 (CRP ≥100 mg/L). Thus, filling each term of the equation with 1 or 0 regarding if the respective condition is present or not, patients can be assigned a probability of critical disease or fatality on the basis of information from the initial history and quickly available laboratory examinations.

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Availability of data and materials

Data are available on request.

Ethics approval

The study protocol was approved by the Ethics Committee of Virgen Macarena and Virgen del Rocío University Hospitals (C.I. 0771-N-20) and complied the Declaration of Helsinki.

Consent for publication

All authors have approved the manuscript and its publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.09.023.

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