WHO Ordinal Scale and Inflammation Risk Categories in COVID-19. Comparative Study of the Severity Scales

Manuel Rubio-Rivas, MD PhD[1], José María Mora-Luján, MD PhD[1], Francesc Formiga, MD PhD[1], Coral Arévalo-Cañas, MD[2], Juan Manuel Lebrón Ramos, MD PhD[3], María Victoria Villalba García, MD[4], Eva Mª Fonseca Aizpuru, MD[5], Jesús Díez-Manglano, MD[6], Francisco Arnalich Fernández, MD PhD[7], Juan Luis Romero Cabrera, MD[8,9], Gema María García García, MD PhD[10], Paula M. Pesqueira Fontan, MD[11], Juan Antonio Vargas Núñez, MD PhD[12], Santiago Jesús Freire Castro, MD[13], José Loureiro Amigo, MD[14], Maria de los Reyes Pascual Pérez, MD[15], José N. Alcalá Pedrajas, MD PhD[16], Daniel Encinas-Sánchez, MD[17], Carmen Mella Pérez, MD[18], Javier Ena, MD[19], Anyuli Gracia Gutiérrez, MD PhD[20], María José Esteban Giner, MD PhD[21], José F. Varona, MD PhD[22,23], Jesús Millán Núñez-Cortés, MD PhD[4], and José-Manuel Casas-Rojo, MD PhD[24] on behalf of the SEMI-COVID-19 Network

[1]Department of Internal Medicine, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, University of Barcelona, Barcelona, Spain; [2]Department of Internal Medicine, 12 de Octubre University Hospital, Madrid, Spain; [3]Department of Internal Medicine, Costa del Sol Hospital, Marbella, Málaga, Spain; [4]Department of Internal Medicine, Gregorio Marañón University Hospital, Madrid, Spain; [5]Department of Internal Medicine, Cabueñes University Hospital, Gijón, Spain; [6]Department of Internal Medicine, Royo Villanova Hospital, Zaragoza, Spain; [7]Department of Internal Medicine, La Paz/Carlos III/Cantoblanco University Hospital, Madrid, Spain; [8]Lipids and Atherosclerosis Unit, Department of Internal Medicine, Maimonides Biomedical Research Institute of Córdoba (IMIBIC), Reina Sofía University Hospital, University of Córdoba, Córdoba, Spain; [9]CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Institute of Health Carlos III (ISCIII), Madrid, Spain; [10]Department of Internal Medicine, Badajoz University Hospital, Badajoz, Spain; [11]Department of Internal Medicine, Santiago de Compostela Clinical Hospital, Santiago de Compostela, La Coruña, Spain; [12]Department of Internal Medicine, Puerta de Hierro University Hospital, Majadahonda, Madrid, Spain; [13]Department of Internal Medicine, A Coruña University Hospital, La Coruña, Spain; [14]Department of Internal Medicine, Moisès Broggi Hospital, Sant Joan Despí, Barcelona, Spain; [15]Department of Internal Medicine, Elda University General Hospital, Elda, Alicante, Spain; [16]Department of Internal Medicine, Pozoblanco Hospital, Pozoblanco, Córdoba, Spain; [17]Department of Internal Medicine, Salamanca University Hospital-IBSAL, Salamanca, Spain; [18]Department of Internal Medicine, Ferrol Clinical University Hospital, Ferrol, La Coruña, Spain; [19]Department of Internal Medicine, Marina Baixa Hospital, Villajoyosa, Alicante, Spain; [20]Department of Internal Medicine, Defense General Hospital, Zaragoza, Spain; [21]Department of Internal Medicine, Virgen de los Lirios Hospital, Alcoy, Alicante, Spain; [22]Department of Internal Medicine, HM Montepríncipe University Hospital, Madrid, Spain; [23]Medicine School, San Pablo-CEU University, CEU Universities, Madrid, Spain; [24]Department of Internal Medicine, Infanta Cristina University Hospital, Parla, Madrid, Spain.

BACKGROUND: The WHO ordinal severity scale has been used to predict mortality and guide trials in COVID-19. However, it has its limitations.

OBJECTIVE: The present study aims to compare three classificatory and predictive models: the WHO ordinal severity scale, the model based on inflammation grades, and the hybrid model.

DESIGN: Retrospective cohort study with patient data collected and followed up from March 1, 2020, to May 1, 2021, from the nationwide SEMI-COVID-19 Registry. The primary study outcome was in-hospital mortality. As this was a hospital-based study, the patients included corresponded to categories 3 to 7 of the WHO ordinal scale. Categories 6 and 7 were grouped in the same category.

KEY RESULTS: A total of 17,225 patients were included in the study. Patients classified as high risk in each of the WHO categories according to the degree of inflammation were as follows: 63.8% vs. 79.9% vs. 90.2% vs. 95.1% ($p<0.001$). In-hospital mortality for WHO ordinal scale categories 3 to 6/7 was as follows: 0.8% vs. 24.3% vs. 45.3% vs. 34% ($p<0.001$). In-hospital mortality for the combined categories of ordinal scale 3a to 5b was as follows: 0.4% vs. 1.1% vs. 11.2% vs. 27.5% vs. 35.5% vs. 41.1% ($p<0.001$). The predictive regression model for in-hospital mortality with our proposed combined ordinal scale reached an AUC=0.871, superior to the two models separately.

CONCLUSIONS: The present study proposes a new severity grading scale for COVID-19 hospitalized patients. In our opinion, it is the most informative, representative, and predictive scale in COVID-19 patients to date.

KEY WORDS: COVID-19; prognosis; WHO ordinal scale; inflammation.

Abbreviations

ARDS	acute respiratory distress syndrome
AUC	area under the curve
BMI	body mass index
COPD	chronic obstructive pulmonary disease

Received September 4, 2021
Accepted March 25, 2022
Published online April 8, 2022

CRP	C-reactive protein
CS	corticosteroids
ECMO	extracardiac membranous oxygenation
HFNC	high-flow nasal cannula
ICU	intensive care unit
IMV	invasive mechanical ventilation
IQR	interquartile range
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
NIMV	noninvasive mechanical ventilation
OSAS	obstructive sleep apnea syndrome
PCR	polymerase chain reaction
RCT	randomized clinical trial
SD	standard deviation
SEMI	Spanish Society of Internal Medicine
TCZ	tocilizumab
WHO	World Health Organization

J Gen Intern Med 37(8):1980–7
DOI: 10.1007/s11606-022-07511-7

INTRODUCTION

COVID-19 is a disease with a viral trigger that causes an inflammatory escalation leading to acute respiratory distress syndrome (ARDS) in some patients.[1] From the beginning of the pandemic, WHO proposed a severity classification based on the respiratory status of patients.[2] This strategy facilitated the therapeutic approach and the prediction of clinical worsening during admission in patients with COVID-19. On the other hand, it also served as a guide for the clinical trials (RCT) of the different therapies that have been proposed during this time.[3]

However, COVID-19 is a particularly clinic-functional-radiological dissociated disease and characteristically produces a well-tolerated hypoxemia that does not reflect the underlying severity. A severity classification strategy has recently been proposed by our group based on the degrees of analytical inflammation.[4]

The present study aimed to compare both strategies and a model based on a combination of both.

METHODS

Study Design, Patient Selection, and Data Collection

This is a retrospective cohort study with data on patients collected and followed up from March 1, 2020, to May 1, 2021, from the nationwide Spanish SEMI-COVID-19 Registry. The characteristics of the patients included in this registry have been extensively described previously.[5] This is a multicenter, nationwide registry with over 150 hospitals registered so far. All included patients were diagnosed by polymerase chain reaction (PCR) test taken from a nasopharyngeal sample, sputum, or bronchoalveolar lavage. The analytical data collected in the present study correspond to the analysis upon admission as well. The collection of data from each patient in terms of laboratory data, treatments, and outcomes was verified by the principal investigator of each center through the review of clinical records.

All participating centers in the register received confirmation from the relevant Ethics Committees, including Bellvitge University Hospital (PR 128/20).

WHO Ordinal Scale

The WHO ordinal clinical severity scale was collected at the time of hospital admission. The 9 points of the scale are as follows: 0: no clinical or virological evidence of infection; 1: ambulatory, no activity limitation; 2: ambulatory, activity limitation; 3: hospitalized, no oxygen therapy; 4: hospitalized, oxygen mask or nasal prongs; 5: hospitalized, noninvasive mechanical ventilation (NIMV) or high-flow nasal cannula (HFNC); 6: hospitalized, intubation and invasive mechanical ventilation (IMV); 7: hospitalized, IMV + additional support such as pressors or extracardiac membranous oxygenation (ECMO); 8: death.

As this was a hospital-based study, the patients included corresponded to categories 3 to 7 of the WHO ordinal scale. Categories 6 and 7 were grouped in the same category because there were few patients in each category and also because of difficulties in differentiating between the two in our database.

Degrees of Inflammation

We previously reported the 3 categories of risk (low, intermediate, and high risk) based on the total lymphocyte count, and the C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer values taken at the time of admission.[4]

Combined Ordinal Scale of Severity

The scale we propose in the present study combines the WHO ordinal scale and the degrees of inflammation. It thus results in 6 categories in hospitalized population by COVID-19 (Fig. 1): 3a: hospitalized, no oxygen therapy and not high risk of inflammation; 3b: hospitalized, no oxygen therapy and high risk of inflammation; 4a: hospitalized, oxygen mask or nasal cannula and not high risk of inflammation; 4b: hospitalized, oxygen mask or nasal prongs and high risk of inflammation; 5a: hospitalized, NIMV, HFNC, IMV, ICU, ECMO, or pressors and not high risk of inflammation; 5b: hospitalized, NIMV, HFNC, IMV, ICU, ECMO, or pressors and high risk of inflammation.

Treatments Prescribed

Regarding antiviral treatment, the use of antivirals (lopinavir/ritonavir,[6] remdesivir[3]), hydroxychloroquine,[7] azithromycin,[7] corticosteroids (CS),[8] and tocilizumab (TCZ)[9–11] was allowed

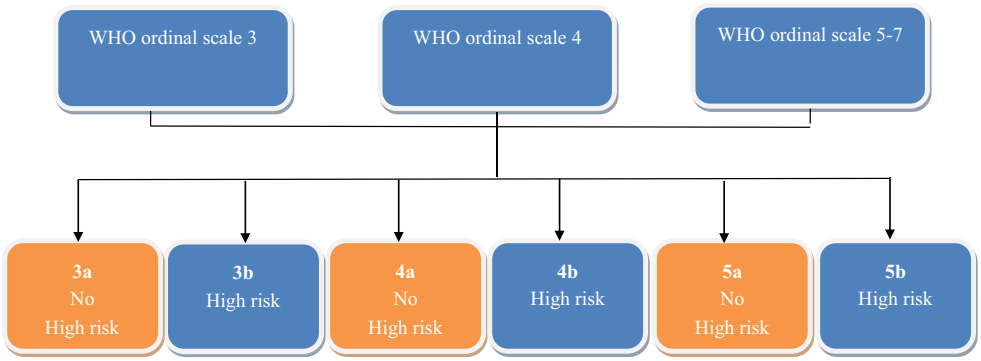

Figure 1 Severity classification algorithm in hospitalized patients with COVID-19 combining the WHO ordinal scale and inflammatory risk categories.

according to the recommendations of the Spanish Ministry of Health.

Outcomes

The primary outcome of the study was in-hospital mortality. Secondary outcomes were the requirement of HFNC, NIMV, IMV, ECMO, and intensive care unit (ICU) admission.

Statistical Analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables are expressed as mean plus standard deviation (SD) in the case of parametric distribution or median [IQR] in the case of non-parametric distribution. Differences among groups were assessed using the chi-square test for categorical variables and ANOVA or Kruskal-Wallis test as appropriate for continuous variables. p values< 0.05 indicated statistical significance.

For the study of risk factors associated with in-hospital mortality, univariate and multivariate binary logistic regression was performed. For the latter, variables with p<0.10 in the univariate study plus age and gender were included. The differences in mortality were shown graphically using Kaplan-Meier curves with their log-rank test (event: death;

Table 1 General Data Between Groups in the WHO Ordinal Scale

	WHO ordinal scale				
	3	**4**	**5**	**6/7**	***p* value**
n	5391	11,438	234	162	
Age, median [IQR]	60.7 [48.8–73.3]	72.3 [60.5–81.9]	68.8 [60–77.7]	63.7 [53.4–72.7]	<0.001
Gender (males), *n* (%)	2803 (52)	6862 (60)	168 (71.8)	118 (72.8)	<0.001
Days from onset to admission, median [IQR]	7 [4–10]	6 [4–9]	7 [4–10]	7 [4–9]	<0.001
BMI, median [IQR]	28 [25–31.7]	28.7 [25.7–32.3]	29.9 [27.1–33.4]	30.2 [26.7–33.1]	<0.001
Race, *n* (%)					<0.001
Caucasian	4582 (85)	10,421 (91.1)	192 (82.1)	138 (85.2)	
Black	46 (0.9)	50 (0.4)	1 (0.4)	0	
Hispanic	639 (11.9)	808 (7.1)	28 (12)	14 (8.6)	
Asian	40 (0.7)	41 (0.4)	3 (1.3)	2 (1.2)	
Others	84 (1.6)	118 (1)	10 (4.3)	8 (4.9)	
Smoking behavior, *n* (%)					<0.001
Never smoker	4060 (75.3)	7691 (67.2)	142 (60.7)	99 (61.1)	
Former smoker	1052 (19.5)	3221 (28.2)	79 (33.8)	52 (32.1)	
Current smoker	279 (5.2)	526 (4.6)	13 (5.6)	11 (6.8)	
Degree of dependency, *n* (%)					<0.001
None or mild	4890 (90.7)	9159 (80.1)	198 (84.6)	158 (97.5)	
Moderate	283 (5.2)	1273 (11.1)	23 (9.8)	3 (1.9)	
Severe	218 (4)	1006 (8.8)	13 (5.6)	1 (0.6)	
Arterial hypertension, *n* (%)	2126 (39.4)	6587 (57.6)	137 (58.5)	79 (48.8)	<0.001
Dyslipidemia, *n* (%)	1760 (32.6)	4967 (43.4)	113 (48.3)	73 (45.1)	<0.001
Diabetes mellitus, *n* (%)	792 (14.7)	2682 (23.4)	66 (28.2)	47 (29)	<0.001
Ischemic cardiopathy, *n* (%)	287 (5.3)	1008 (8.8)	13 (5.6)	11 (6.8)	<0.001
Chronic heart failure, *n* (%)	185 (3.4)	900 (7.9)	16 (6.8)	5 (3.1)	<0.001
Chronic liver disease, *n* (%)	169 (3.1)	416 (3.6)	6 (2.6)	4 (2.5)	0.281
Severe chronic renal failure, *n* (%)	206 (3.8)	755 (6.6)	16 (6.8)	3 (1.9)	<0.001
Dementia, *n* (%)	283 (5.2)	1338 (11.7)	8 (3.4)	2 (1.2)	<0.001
Cancer, *n* (%)	406 (7.5)	1143 (10)	17 (7.3)	7 (4.3)	<0.001
COPD, *n* (%)	164 (3)	965 (8.4)	22 (9.4)	10 (6.2)	<0.001
Asthma, *n* (%)	409 (7.6)	759 (6.6)	16 (6.8)	16 (9.9)	0.064
OSAS, *n* (%)	218 (4)	797 (7)	24 (10.3)	16 (9.9)	<0.001
Charlson index, median [IQR]	0 [0–1]	1 [0–2]	1 [0–2]	0 [0–1]	<0.001

IQR interquartile range, BMI body mass index

Table 2 Lab Tests Upon Admission Between Groups in the WHO Ordinal Scale

	WHO ordinal scale				
	3	4	5	6/7	*p* value
PaO_2/FiO_2, median [IQR]	322 [265–378]	286 [230–338]	227 [133–300]	241 [151–287]	<0.001
Lymphocytes $\times 10^6$/L, median [IQR]	1090 [800–1460]	900 [620–1200]	825 [580–1115]	745 [529–1093]	<0.001
CRP mg/L, median [IQR]	39 [12–88]	78 [30–146]	131 [75–220]	141 [79–228]	<0.001
LDH U/L, median [IQR]	288 [226–378]	342 [262–462]	414 [326–523]	445 [334–600]	<0.001
Ferritin mcg/L, median [IQR]	522 [179–1191]	785 [300–1494]	1203 [577–1867]	1027 [433–1734]	<0.001
D-dimer ng/mL, median [IQR]	546 [275–1170]	700 [350–1586]	596 [316–1210]	725 [430–1372]	<0.001
Risk categories of inflammation, *n* (%)					
Low risk	313 (5.8)	178 (1.6)	1 (0.4)	0	<0.001
Intermediate risk	1638 (30.4)	2119 (18.5)	22 (9.4)	8 (4.9)	<0.001
High risk	3440 (63.8)	9141 (79.9)	211 (90.2)	154 (95.1)	<0.001

CRP C-reactive protein, LDH lactate dehydrogenase, IQR interquartile range

censored data: hospital discharge). Missing data were treated with multiple imputations.

Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA: IBM Corp.

RESULTS

General Data and Symptoms Between Groups

A total of 21,962 patients were included in the Registry by May 2021. Of these, 17,225 patients had community (non-nosocomial) COVID-19 infection and their baseline oxygenation data were collected in the database for inclusion in the present study (Figure S1). Table 1 shows the differences in overall baseline data between the different WHO severity categories. Table 1 shows the differences in overall baseline data between the different WHO severity categories.

Symptoms at the time of hospital admission are shown in Table S1. WHO category 3 presented less frequently dyspnea (48.9% vs. 62.7% vs. 88.9% vs. 80.2%; $p<0.001$) as well as tachypnea at admission (18.6% vs. 36.9% vs. 72.2% vs. 75.3%; $p<0.001$). On the contrary, they presented more frequently arthromyalgia (35.4% vs. 28.1% vs. 26.5% vs. 29.6%; $p<0.001$), ageusia (13.4% vs. 7.4% vs. 12.8% vs. 9.3%; $p<0.001$), anosmia (12.2% vs. 6.2% vs. 13.2% vs. 8%; $p<0.001$), sore throat (11.7% vs. 8.4% vs. 6% vs. 8%; $p<0.001$), and headache (15.9% vs. 10.7% vs. 9.8% vs. 11.1%; $p<0.001$).

Lab Tests Between Groups

Table 2 shows the analytical parameters between the different WHO categories. As expected, the higher the severity, the lower the PaO_2/FiO_2 and lymphocyte count and the higher the CRP, LDH, and ferritin. It is noteworthy that between WHO categories 5 and 6/7 this progression in the analytical figures was not observed. As for D-dimer, differences were observed between the 4 groups but the differences were not progressive in parallel to the severity on the scale.

The patients classified as high risk in each of the WHO categories according to the degree of inflammation were as follows: 63.8% vs. 79.9% vs. 90.2% vs. 95.1% ($p<0.001$) (Table 2; Fig. 2). The high-risk parameters elevated in each of the WHO categories are detailed in Table S2. Likewise, the correlation between the WHO

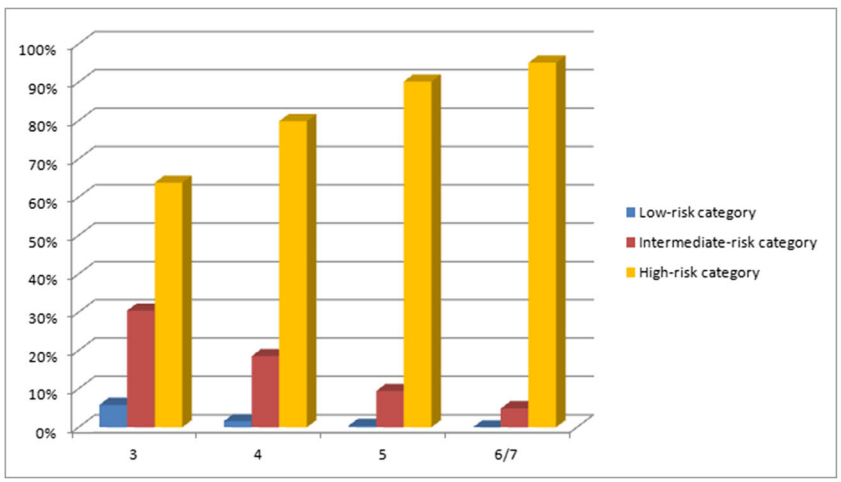

Figure 2 Risk categories of inflammation by the WHO ordinal scale.

Table 3 Outcomes Between Groups in the WHO Ordinal Scale and the Combined Ordinal Scale

	WHO ordinal scale						
	3		4	5		6/7	*p* value
Primary outcome, *n* (%)							
In-hospital mortality	45 (0.8)		2774 (24.3)	106 (45.3)		55 (34)	<0.001
Secondary outcomes, *n* (%)							
HFNC	108 (2)		1305 (11.4)	195 (83.3)		80 (49.4)	<0.001
NIMV	37 (0.7)		815 (7.1)	138 (59)		51 (31.5)	<0.001
IMV	29 (0.5)		1086 (9.5)	71 (30.3)		110 (67.9)	<0.001
ICU admission	50 (0.9)		1382 (12.1)	87 (37.2)		162 (100)	<0.001
ECMO	3 (0.1)		13 (0.1)	4 (1.7)		2 (1.2)	<0.001
	Combined ordinal scale						
	3a	**3b**	**4a**	**4b**	**5a**	**5b**	***p* value**
Primary outcome, *n* (%)							
In-hospital mortality	7 (0.4)	38 (1.1)	258 (11.2)	2516 (27.5)	11 (35.5)	150 (41.1)	<0.001
Secondary outcomes, *n* (%)							
HFNC	23 (1.2)	85 (2.5)	173 (7.5)	1132 (12.4)	21 (67.7)	254 (69.6)	<0.001
NIMV	6 (0.3)	31 (0.9)	114 (5)	701 (7.7)	11 (35.5)	178 (48.8)	<0.001
IMV	6 (0.3)	23 (0.7)	110 (4.8)	976 (10.7)	5 (16.1)	176 (48.2)	<0.001
ICU admission	9 (0.5)	41 (1.2)	155 (6.7)	1227 (13.4)	12 (38.7)	237 (64.9)	<0.001
ECMO	0	3 (0.1)	1 (0.1)	12 (0.1)	0	6 (1.6)	<0.001

HFNC high-flow nasal cannula, NIMV noninvasive mechanical ventilation, IMV invasive mechanical ventilation, ICU intensive care unit, ECMO extracardiac membranous oxygenation

clinical severity categories and the inflammatory parameters is detailed in Table S3.

Treatments Between Groups

As expected, those treatments with greater evidence of effectiveness (CS, TCZ, remdesivir, and heparin) were more frequently used in higher severity categories (Table S4).

Outcomes Between Groups

The outcomes are shown in Table 3 and Figure S2–4. The first part of the table shows the outcomes for each of the WHO severity categories. In-hospital mortality for categories 3 to 6/7 was as follows: 0.8% vs. 24.3% vs. 45.3% vs. 34% (p<0.001). The second part of the table shows the outcomes for the proposed combined scale with degrees of inflammation and WHO categories. In-hospital mortality for categories 3a to 5b was as follows: 0.4% vs. 1.1% vs. 11.2% vs. 27.5% vs. 35.5% vs. 41.1% (p<0.001). Survival between the different categories in the proposed model is depicted in Figure 3.

Risk Factors for In-Hospital Mortality

Table 4 shows the results of the multivariate analysis of the 3 models (degrees of inflammation vs. WHO vs. combined model). In the previous univariate study, age, sex, BMI, race, smoking behavior, degree of dependency, different comorbidities, Charlson index, tachypnea upon admission,

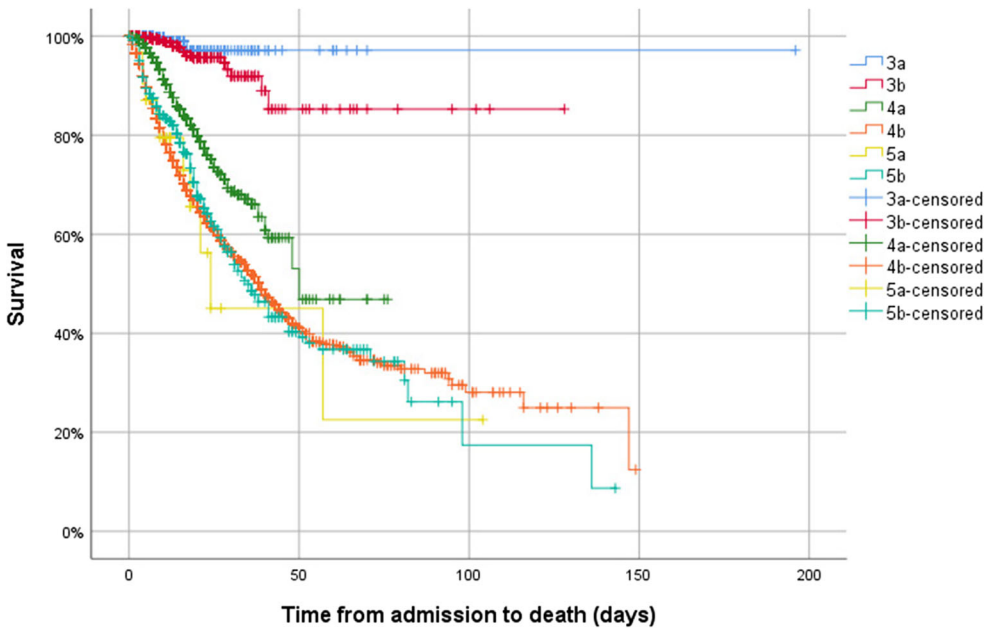

Figure 3 Kaplan-Meier curves of the combined ordinal scale of severity. Log-rank test=936.76, p<0.001.

Table 4 Risk Factors for In-Hospital Mortality Based on the Categories of Inflammation vs. WHO Ordinal Scale. Multivariate Analysis

	Model based on the risk categories of inflammation		Model based on the WHO ordinal scale		Model including the WHO scale and categories of inflammation	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.07 (1.06–1.07)	<0.001	1.07 (1.06–1.07)	<0.001	1.07 (1.06–1.07)	<0.001
Gender (female)	0.65 (0.59–0.72)	<0.001	0.66 (0.60–0.73)	<0.001	0.70 (0.63–0.77)	<0.001
BMI	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Race	NS		NS		NS	
Caucasian (ref.)						
Black						
Hispanic						
Asian						
Others						
Dependency						
No	1 ref.		1 ref.		1 ref.	
Moderate	1.46 (1.27–1.67)	<0.001	1.45 (1.26–1.67)	<0.001	1.49 (1.29–1.72)	<0.001
Severe	1.92 (1.65–2.23)	<0.001	1.90 (1.62–2.22)	<0.001	1.98 (1.70–2.32)	<0.001
Arterial hypertension	NS		NS		NS	
Dyslipidemia	NS		NS		NS	
Diabetes mellitus	NS		NS		NS	
Ischemic cardiopathy	1.19 (1.02–1.38)	0.024	1.24 (1.06–1.44)	0.007	1.25 (1.07–1.46)	0.005
Chronic heart failure	NS		NS		NS	
Chronic liver disease	NS		NS		NS	
Severe chronic renal failure	NS		NS		NS	
Dementia	NS		NS		NS	
Cancer	NS		NS		NS	
COPD	NS		NS		NS	
Asthma	0.74 (0.60–0.90)	0.003	0.69 (0.56–0.85)	<0.001	0.72 (0.58–0.88)	0.002
OSAS	NS		NS		NS	
Charlson index	1.14 (1.12–1.17)	<0.001	1.16 (1.13–1.19)	<0.001	1.15 (1.12–1.18)	<0.001
Respiratory rate >20 rpm	2.77 (2.53–3.04)	<0.001	2.52 (2.29–2.77)	<0.001	2.37 (2.16–2.61)	<0.001
Tocilizumab	1.83 (1.59–2.11)	<0.001	1.57 (1.36–1.81)	<0.001	1.53 (1.32–1.76)	<0.001
Corticosteroids	1.49 (1.35–1.64)	<0.001	1.29 (1.17–1.42)	<0.001	1.24 (1.13–1.38)	<0.001
Remdesivir	0.50 (0.40–0.64)	<0.001	0.43 (0.34–0.55)	<0.001	0.45 (0.36–0.58)	<0.001
Categories of risk			-			
Low risk	1 ref.				1 ref.	
Intermediate risk	1.81 (1.02–3.22)	0.044			1.55 (0.85–2.83)	0.153
High risk	5 (2.85–8.77)	<0.001			3.95 (2.19–7.10)	<0.001
WHO ordinal scale	-					
3			1 ref.		1 ref.	
4			21.9 (16.2–29.6)	<0.001	20.9 (15.4–28.2)	<0.001
5			65.3 (42.8–99.5)	<0.001	60.4 (39.6–92.2)	<0.001
6/7			60.7 (38–96.8)	<0.001	53.4 (33.4–85.3)	<0.001
AUC	0.840		0.866		0.871	

AUC area under curve, BMI body mass index, NS not significant, COPD chronic obstructive pulmonary disease, OSAS obstructive sleep apnea syndrome

and the use of different therapies (CS, TCZ, and remdesivir) were analyzed. All of them were significant in the univariate study so they were entered in the multivariate models.

The in-hospital mortality predictive model that included the degrees of inflammation reached an area under the curve (AUC) of 0.840. The model that included the WHO severity categories reached an AUC=0.866. The model that included both variables reached an AUC=0.871. Table S5 shows the regression model with our proposal combined with categories 3a to 5b. The AUC of this model was also 0.871 (Figure S5).

DISCUSSION

In the present study, we demonstrate and propose a new and better method of classifying the clinical severity of patients admitted for COVID-19 according to respiratory status and degrees of analytical inflammation. We believe that it is more in line with reality and better defines subgroups of patients who were previously grouped in the same category. It also allows progress to be made in therapeutic strategies since it identifies patients at risk without waiting for subsequent respiratory deterioration.

Several severity scores have been proposed in the last 2 decades to assess community-acquired pneumonia severity: Pneumonia Severity Index (PSI),[12] CURB-65,[13] A-DROP,[14] SMART-COP,[15] NEWS2,[16] and qSOFA.[17] They focus on the respiratory state and organ failure. They were not developed for COVID-19 and, therefore, the inflammatory response is not represented in them. Thus, and although the AUC is high for some of them as predictive tool in COVID-19,[18] it is not a good tool in some inflamed patients with not yet impaired respiratory condition. Besides, these scores cannot lead trials focused on immunosuppressants in COVID-19. The WHO severity scale has been a good classifying and predictive tool

for patients with COVID-19.[2] However, it has some shortcomings that should be recalled. On the one hand, category 4 defines patients hospitalized in a conventional ward with oxygen therapy. Obviously, a patient with nasal cannula at 2 L per minute is not the same as a patient with a 50% mask or with a reservoir, but in this classification they are included in the same group. On the other hand, and as we showed in our article, categories 5-6-7 do not differ so much in their basal and analytical characteristics and in their outcomes, and neither are these progressive.[4] Besides, we cannot forget it is not a validated scale. For this reason, we believe that these subcategories are informative of the resources used but do not provide added informative value of their clinical, analytical, or predictive characteristics and, therefore, should be grouped in the same category. Finally, the predictive leap in in-hospital mortality between categories 3 and 4, and subsequently 4 and 5, is very large. This means that, for simplicity's sake, there are groups of patients that have been grouped with others and are not completely well represented.

The alternative model based on degrees of inflammation is a different approach to the disease and its severity.[4] It has the advantage of being able to identify patients at high risk who have not yet presented respiratory deterioration. In this sense, Figure S1 shows how in categories with mild and moderate disease there are about 60% and 80%, respectively, of patients characterized as high risk according to analytical degrees of inflammation.

The model we propose is a combination of both models. It is more informative and representative of the real severity of each patient. In addition, the multivariate study performed shows a slightly higher AUC than the other 2 models. Not only should it be a practical tool for clinical use, but we believe it should be the basis for RCTs, many of which have failed for these reasons. Especially those RCTs assessing immunosuppressants such as CS and TCZ without including and defining patient inflammation well could have benefited greatly from this clinical-analytical approach.[8–11]

The advantage of a model based on degrees of inflammation is the fact that the escalation of inflammation precedes respiratory deterioration. Thus, clinicians can detect earlier those patients susceptible to clinical worsening in the following days. On the other hand, COVID-19 is a clinico-functional-radiological dissociated disease. Thus, a patient with significant hypoxemia can tolerate it acceptably without requiring additional ventilatory resources as in other diseases. It can also guide the anti-inflammatory/immunosuppressive therapies accepted in the treatment of COVID-19. Certainly, not all patients die from the accompanying inflammation of the disease; there are other accompanying predictive variables and, therefore, the WHO classification based on respiratory status and oxygen/ventilation support also provides predictive power. Surely this combination is what makes the hybrid model the most complete and predictive.

Our study has some obvious strengths. The patient sample is very large and comes from a wide range of hospitals of all types nationwide. The database is very large and includes numerous clinical and analytical variables at the time of hospital admission.

Our study also has some limitations that deserve comment. First, it is a retrospective study. Second, being a multicenter study, it gives a good idea of what COVID-19 has been in our country but introduces a certain degree of heterogeneity when it comes to including the data.

In conclusion, the present study proposes a new severity classification scale for patients hospitalized by COVID-19. In our opinion, it is the most informative, representative, and predictive scale in COVID-19 patients to date.

Supplementary Information *The online version contains supplementary material available at https://doi.org/10.1007/s11606-022-07511-7.*

Acknowledgements: *We gratefully acknowledge all the investigators who participated in the SEMI-COVID-19 Registry. We also thank the SEMI-COVID-19 Registry Coordinating Center for their quality control data, logistic, and administrative support.*

Corresponding Author: *Manuel Rubio-Rivas, MD PhD; Department of Internal Medicine, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, University of Barcelona, Barcelona, Spain (e-mail: mrubio@bellvitgehospital.cat).*

Declarations:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

REFERENCES

1. Hu B, Huang S, Yin L. The Cytokine Storm and COVID-19. J Med Virol. 2020 Jun 27;https://doi.org/10.1002/jmv.26232. Online ahead of print.
2. World Health Organization. WHO R&D Blueprint Novel Coronavirus COVID-19 Therapeutic Trial Synopsis 2020a, available at https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 - final report. N Engl J Med. 2020; 383: 1813-26.
4. Rubio-Rivas M, Corbella X, Formiga F, et al. Risk categories in COVID-19 based on degrees of inflammation: data on more than 17,000 patients from the Spanish SEMI-COVID-19 Registry. J Clin Med. 2021; 10: 2214.
5. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. Rev Clin Esp. 2020; 220: 480-94.
6. Lora-Tamayo J, Maestro G, Lalueza A, et al. Early lopinavir/ritonavir does not reduce mortality in COVID-19 patients: results of a large multicenter study. J Infect. 2021: S0163-4453(21)00077-3.
7. Gautret P, Hoang VT, Lagier JC, Raoult D. Effect of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, an update with an intention-to-treat analysis and clinical outcomes. Int J Antimicrob Agents. 2021; 57: 106239.
8. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021; 384: 693-704.
9. Rubio-Rivas M, Ronda M, Padulles A, et al. Beneficial effect of corticosteroids in preventing mortality in patients receiving tocilizumab to treat severe COVID-19 illness. Int J Infect Dis. 2020; 101: 290-7.
10. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med. 2021 Feb 25:NEJMoa2100433. https://doi.org/10.1056/NEJMc2108482
11. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397:1637-45.

12. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336: 243–250.
13. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58: 377–382.
14. Miyashita N, Matsushima T, Oka M, et al. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med 2006; 45: 419–428.
15. Charles PGP, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis 2008; 47: 375–384.
16. National Health Service (NHS) England. Resources to support the safe adoption of the revised National Early Warning Score (NEWS2) n.d.. www.england.nhs.uk/wp-content/uploads/2019/12/Patient_Safety_Alert_-_adoption_of_NEWS2.pdf Date last updated: 25 April 2018; date last accessed: 2 April 2020.
17. Rudd KE, Seymour CW, Aluisio AR, et al. Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low- and middle-income countries. JAMA 2018; 319: 2202–2211.
18. Fan G, Tu C, Zhou F, et al. Comparison of severity scores for COVID-19 patients with pneumonia: a retrospective study. Eur Respir J. 2020 Sep 10;56(3):2002113.