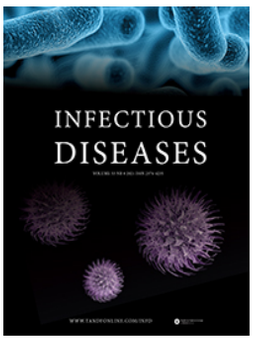

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LETTER TO THE EDITOR

Prospective validation and comparison of COVID-GRAM, NEWS2, 4C mortality score, CURB-65 for the prediction of critical illness in COVID-19 patients

To the editor,

When a patient is hospitalizated with COVID-19, prediction of the risk of development of severe or critical illness is of great importance [1]. Several risk scores have been described such as COVID-GRAM [2], National Early Warning Score 2 (NEWS 2) [3] and 4C mortality score [4]. Gidari *et al* [3] recently demonstrated, in this journal, the accuracy of NEWS2 in predicting patients who will require admission to intensive care unit. However, this score was validated in a small cohort of patients and external validation was required. We here report our efforts to validate all these score and compare them with regard to development of critical disease and poor outcome. We also compare these scores with a simple and cheap biomarker, Neutrophil to Lymphocyte Ratio (NLR) which has been also associated with severe COVID-19 [5].

This prospective observational study was performed in a Belgian teaching hospital (Cliniques Universitaires Saint-Luc). Between 01 october 2020 and 25 december 2020, data from all hospitalized adult patients with confirmed COVID-19 pneumonia in the internal medicine dedicated COVID-19 ward were recorded. The diagnosis of SARS-CoV-2 infection was made by polymerase chain reaction (PCR) on nasopharyngeal swab. We only included in the final analysis patients under oxygen therapy and treated by dexamethasone. Patients receiving chemotherapy, for haematological disease or cancer, were excluded from the study since NLR is difficult to interpret in that context

The following risk scores were prospectively calculated upon admission (CURB-65, COVID-GRAM, NEWS2, 4C mortality score). Depending on the results of the scores, patients were classified into three groups: low risk, moderate risk and high risk score. A fourth group (very high risk) was only used for 4C mortality score since this score included 4 categories. The study was approved by our local ethical committee (CEHF 2020/06AVR/201).

All analyses were conducted using SPSS 27 software (BM SPSS Statistics for Windows, Version 27.0, Armonk, NY: IBM Corp). Continuous variables were expressed as mean and standard deviation and categorical variables as counts and percentages. Categorical variables were analysed using Chi-squared test or Fisher's exact test. Continuous variables were analysed using unpaired *t*-test. In order to find risk factors for overall survival, a logistic regression technique was used and odds ratio were reported. Receiver operating characteristic (ROC) curves were generated. All tests were 2-sided, with 5 percent as significance threshold.

In total, 114 patients were admitted to our department, of whom 101 were included in the final analysis (13 patients were excluded from the study: 7 patients were not requiring oxygen therapy, 2 patients were under chemotherapy and 4 were not receiving dexamethasone). Mean age was 62 years and the male to female ratio was 62/39. The rate of ICU admission and death was 17.8% and 18.8% respectively. Among patients admitted to intensive care unit, 50% were intubated and 100% of patients required high flow nasal canula. The most frequent symptoms on admission were shortness of breath (94%), cough (78.2%), general weakness (49.5%), myalgia (33.6%), headache (24.7%), diarrhoea (14.8%), ageusia (14.8%) and anosmia (11.8%). The most frequent comorbidities were cardiovascular diseases (44.5%), hypertension (51.4%), diabetes (21.7%), immunodeficiency (17.8%), chronic kidney disease (15.8%) and chronic pulmonary diseases (9.9%). The rate of patients under non-mechanical support such as oxygen mask and CPAP was 54.4% and 42.5% respectively.

As shown in Table 1, the rate of all death was significantly ($p < 0.05$) associated with the severity of the risk score (NEWS2, 4C mortality score, CURB-65, COVID-GRAM and NLR on admission) while the rate of ICU

Table 1. Rate of ICU admission and overall death in hospitalized patients with COVID19 according to different risk scores and NLR.

Variable	ICU admission No ($n = 85$)	Yes ($n = 16$)	p Value	Overall death No ($n = 82$)	Yes ($n = 19$)	p Value
NLR on admission	7.1 (6.3)	7.8 (5)	.69	11.2 (6)	6.3 (5)	<.001
CURB-65						
1	55 (65%)	10 (62%)	.23	60 (73)	5 (26)	.001
2	20 (23)	6 (38)		16 (20)	10 (53)	
3	10 (12)	0		6 (7)	4 (21)	
NEWS2						
1	31 (36)	0	.009	29 (35)	2 (10)	.005
2	27 (32)	6 (37)		29 (35)	4 (21)	
3	85 (31)	16 (62)		24 (29)	13 (68)	
COVID-GRAM						
1	6 (7)	0	.25	6 (7)	0	.001
2	43 (51)	6 (37)		46 (56)	3 (16)	
3	36 (42)	10 (65)		30 (36)	16 (84)	
4C mortality						
1	12 (14)	0	.084	12 (15)	0	<.001
2	28 (33)	3 (19)		29 (35)	2 (10)	
3	31 (36)	11 (69)		35 (43)	7 (37)	
4	14 (16)	2 (12)		6 (7)	10 (52)	

1: low risk; 2: mild risk; 3: high risk; 4: very high risk; NLR: neutrophil to lymphocyte ratio; ICU: intensive care unit.

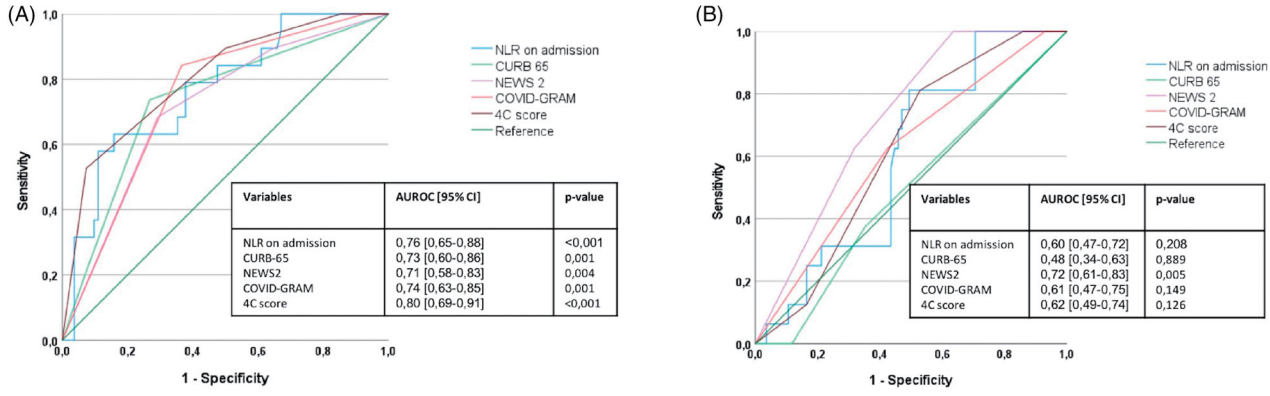

Figure 1. ROC curves showing efficacy of risk scores to predict mortality (A) and intensive care unit admission (B).

admission was mainly significant with NEWS2 and 4C mortality scores. Univariate analysis showed that COVID-GRAM (odds ratio [OR] 8.4; 95% confidence interval [CI] 2.33–30.78; p .001), NEWS2 (OR 7.85; CI 1.61–38.28; p .01), CURB-65 (OR 8; CI 1.68–38.1; 0.009) and 4C mortality score (OR 5.8; CI 2.41–14.2; $p < .001$) were predictive of mortality as well as NLR on admission (OR 1.12; CI 1.03–1.21; p .006). NEWS2 was the only score who was predictive of ICU admission (OR 3.37, CI 1.42–7.96; p .006).

Receiver-operating characteristic (ROC) curves were performed to evaluate the efficacy of these scores and NLR on admission to predict mortality and ICU admission (Figure 1(a,b)). NEWS2 showed strong predictive accuracy for ICU admission and mortality with an area under the ROC (AUROC) curve of 0.72 (p .005) and 0.71 (p .004) respectively. 4C mortality score, COVID-GRAM, CURB-65 and NLR on admission showed strong predictive accuracy for mortality with an AUROC curve of 0.80 ($p <.001$), 0.74 (p .001), 0.74 (p .001) and 0.76 ($p < .001$) respectively.

Our study showed that NEWS2, COVID-GRAM, 4C mortality score, CURB-65 are all helpful in evaluation of risk for mortality and to identify patients at risk of critical illness upon hospital admission. 4C mortality score showed the highest discrimination for mortality prediction, which is in line with previous studies [4, 6]. Moreover, NEWS2 on admission seems to be a better predictor of ICU admission compared to COVID-GRAM, 4C mortality score and CURB-65 as published in Gidari and Myrstad *et al* studies [3, 7]. Compared to the four scores, NLR on admission was also a good predictor of in –hospital mortality. However NLR was not a good predictor of ICU admission. Recently, Simadibrata *et al*

showed that high NLR levels on admission were also associated with severe COVID-19 and mortality in a recent meta-analysis [5].

The present prospective study confirmed the usefulness of 4C, NEWS2, COVID-GRAM, CURB-65 and NLR to predict mortality in COVID-19 hospitalized patients. Interestingly, among them, NEWS2 was a better predictor score for ICU admission.

Disclosure statement

All authors confirmed that there are no conflict of interest.

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