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Commentary

Early prediction of the risk of severe coronavirus disease 2019: A key step in therapeutic decision making

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COVID-19 is caused by the SARS-COV-2 virus and leads to primarily respiratory symptoms. So far, a wide range of clinical manifestations have been reported from complete lack of symptoms to life-threatening multiple organ failure. Currently, therapeutic management is mainly supportive and primarily driven by the presence and severity of an individual's symptoms. It is becoming increasingly obvious that a substantial proportion of patients initially presenting with mild symptoms are at increased risk of developing severe disease and would benefit from early and more aggressive intervention. There is thus a need to develop and validate risk stratification models that can provide early prediction of those individuals who are at risk of developing a severe disease.

In an article published in the July issue of *EBioMedicine, Xiao* et al. propose a novel risk score for this purpose; the HNC-LL score [1]. Specifically, the HNC-LL score includes hypertension, neutrophil count, C-Reactive Protein (CRP), lymphocyte count, and lactate dehydrogenase. Their retrospective study included 690 patients from hospitals in Honghu and Nanchang, China. The stratification results showed good accuracy (Area under the Receiver Operating Characteristic curve >0.85) to predict severe disease in both the training and validation cohorts. The main strength is the simplicity of application in the clinical setting, whereby it has the advantage of including a small number of parameters that are easily and routinely measured in hospitalized patients with respiratory infections. Furthermore, the HNC-LL appears to outperform comparable scores that have been proposed during the COVID-19 pandemic, such as the CURB-65 score (confusion, urea, respiratory rate, blood pressure, 65 years), the MuLBSTA score (multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hypertension, and age) and the neutrophil-to-lymphocyte ratio. Importantly, the HNC-LL score also had a good predictive ability to identify those patients who were admitted to hospital with mild disease and progressed to a severe disease during their hospital stay.

The timing of the risk stratification process in the course of the disease for each individual patient is critical. In the present study, the blood sampling and assessment of risk factors used to determine the HNC-LL risk score were performed on the day of hospital admission. However, patients likely presented to the hospital at different stages of their disease. The delay between the onset of symptoms and the medical examination is a key factor to consider as it provides an estimation of the stage of disease, which was not taken into account in the study by *Xiao* et al. [1]

Another limitation of the HNC-LL, CURB-65 or MuLBSTA scores is that they require blood sampling [2,3], which limit their utilisation for non-hospitalized patients with mild or moderate symptoms. A recent study reported that 21% of COVID-19 patients initially considered to be at low risk, in fact, had poor outcomes [4]. One potential solution to optimize the risk stratification process would be to use different scores adapted to the setting and the timing of the patient presentation. Hence, in an outpatient setting, where patients would generally be at an earlier stage of the disease, clinical scores such as the CRB-65 (CURB-65 without urea) or the qSOFA score (quick sepsis-related organ failure assessment) could be considered [5]. Given that these scores are usually utilized in the context of severe disease, lower cut-off values should likely be applied to improve their sensitivity to identify the patients being at risk of hospitalization and complications (Fig. 1). Another way to potentially improve the performance of those risk scores in the management of COVD-19 would be to include clinical factors proven relevant to affected patients (Fig. 1). Indeed, a striking difference of SARS-COV-2 infection compared to other respiratory viral infections is that cardiometabolic comorbidities have been over-represented in patients presenting complications, while other pulmonary comorbidities that are usually more prevalent with respiratory viral infections such as asthma, smoking, or COPD are under-represented. In the study of *Xiao* et al. hypertension was included into the risk score but not obesity or diabetes [1], which have previously been shown to be strongly associated with poor outcomes in patients with COVID-19 [6].

The set of variables included in the final score by *Xiao* et al. presents several limitations and pitfalls that warrant discussion. First, the authors included two markers of white blood cells, which may, to some extent be redundant. It also likely suggests that patients had been infected for several days and had developed a bacterial infection rendering the neutrophil count significant. The complications and adverse events associated with COVID-19 are

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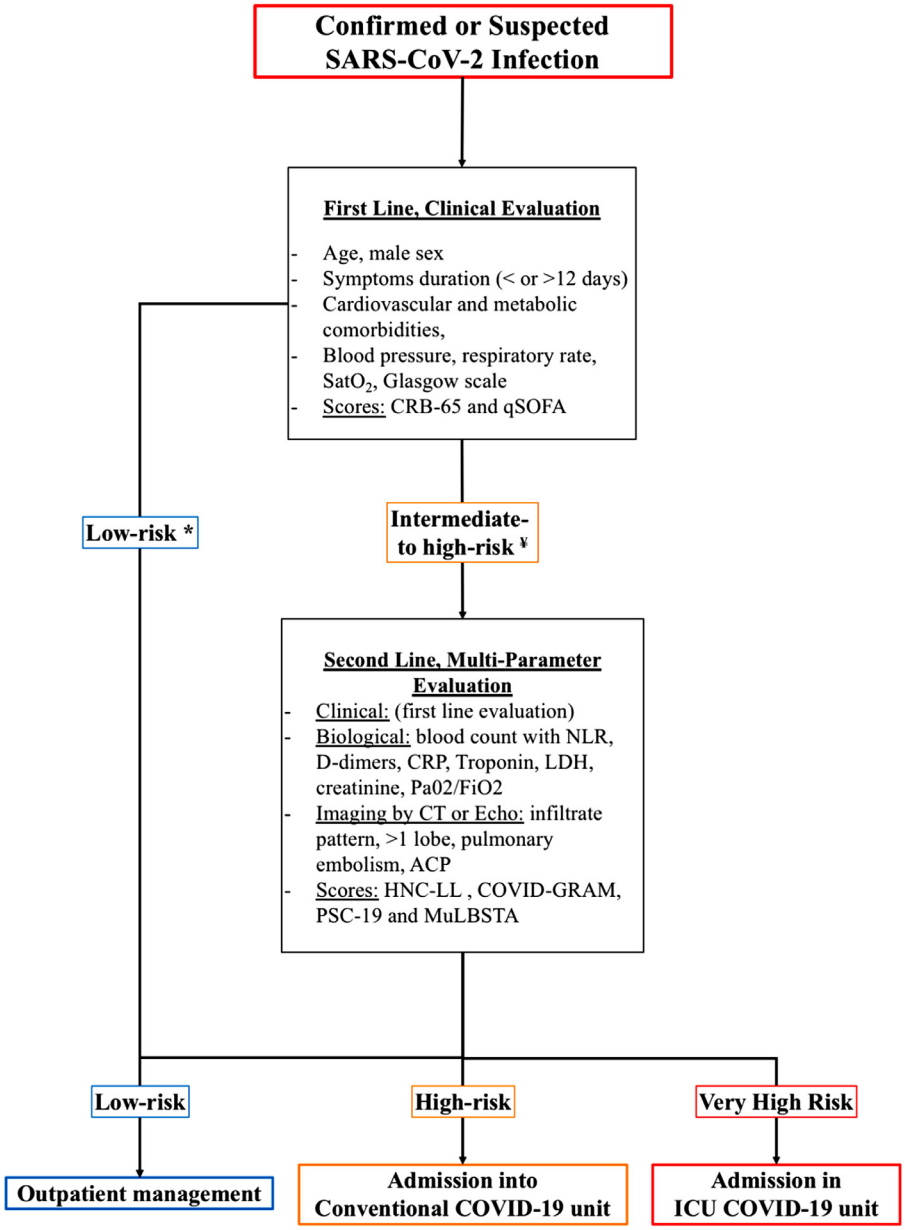

Fig. 1. Integrative Stepwise Approach for the Management of COVID-19.
Abbreviations used: ACP: acute cor pulmonale, COVID-19: coronavirus disease 2019, CRB-65: confusion, respiratory rate, blood pressure, 65 years, CRP: C-reactive protein, CT: computed tomography, Fi02: fraction of inspired oxygen, HNC-LL: hypertension, neutrophil count, CRP, lymphocyte count, and LDH, ICU: intensive care unit, LDH: lactate dehydrogenase, MuLBSTA: multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hypertension, and age, NLR: neutrophil-to-lymphocyte ratio, Pa02: partial pressure of arterial oxygen, PSC-19: predicted score for COVID-19, qSOFA: quick sepsis-related organ failure assessment, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, $Sat0_2$: oxygen saturation. *indicates patients without clinical abnormalities including CRB-65 and qSOFA scores = 0. ¥indicates patients with ≥1 clinical abnormalities including CRB-65 and qSOFA scores ≥1.

generally related to inflammation and the ensuing "cytokine storm", thromboembolism, and cardiac damage. Previous studies have reported that an important proportion (>20%) of hospitalized patients with COVID-19 present with a marked elevation of circulating biomarkers of inflammation (CRP, Ferritin), cardiovascular damage (Troponin) and thrombo-embolism (D-Dimers), identifying subgroups of patients at high risk of in-hospital morbidity and mortality [7-9]. The authors included CRP, but did not include other potentially valuable blood biomarkers, such as D-Dimers, Troponin and Ferritin. The proportion of these high-risk patients is relatively small but there is, nonetheless, a need to identify them early in the course of the disease to enable timely and individualized interventions, such as anti-inflammatory or anti-thrombotic pharmacotherapy. To this point, preliminary analyses of the RECOVERY trial data suggest that treatment with dexamethasone reduces mortality by ~30% in COVID-19 hospitalized patients with supplemental oxygen [10]. Predictive scores that include blood biomarkers of inflammation may help to target the subset of patients who should receive dexamethasone or other anti-inflammatory therapy at an early stage of the disease and could aid in the optimal design of new therapeutic trials.

With the COVID-19 pandemic, the world is currently facing a major health crisis. An integrative multi-parameter stepwise approach, such as the one we propose in Fig. 1, may help to optimize the management of patients with COVID-19. The HNC-LL score proposed by Xiao et al. in *EBioMedicine* is a promising development but needs to be further validated in other independent patient cohorts in other countries and in larger cohorts with mild disease who are not

yet hospitalized. Furthermore, the addition of other relevant parameters, symptom duration and other blood biomarkers (e.g. Ferritin, D-Dimers or Troponin) should be explored to determine whether this would improve the predictive value of the risk score. Another promising approach to rationalize and optimize the risk stratification scores for COVID-19 is to use artificial intelligence and machine learning to select and include the most powerful and informative clinical factors and blood biomarkers into the final score. Developing an easily applicable and reliable clinical tool to predict patient outcome at an early disease stage may dramatically improve the management of patients, while ensuring optimal and rationale utilization of health care resources and providers.

Author contributions

AC prepared the first complete draft of the commentary. JT performed literature search, made critical revisions in the manuscript, and prepared the first draft of the figure. PP made critical revisions on the manuscript and the figure.

Declaration of Competing Interests

Authors have nothing to disclose.

References

[1] Xiao LS, Zhang WF, Gong MC, et al. Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019. EBio Med 2020;57 (102880) Access available: https://doi.org/10.1016/j.ebiom.2020.102880.
[2] Rivera-lzquierdo M, Del Carmen Valero-Ubierna M, Rd JL, et al. Sociodemographic, clinical and laboratory factors on admission associated with COVID-19 mortality in hospitalized patients: a retrospective observational study. PLoS ONE 2020;15(6):e0235107.
[3] Guo L, Wei D, Zhang X, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: the MuLBSTA Score. Front Microbiol 2019;10:2752.
[4] Nguyen Y, Corre F, Honsel V, et al. Applicability of the CURB-65 pneumonia severity score for outpatient treatment of COVID-19. J Infect 2020.
[5] Su Y, Tu GW, Ju MJ, et al. Comparison of CRB-65 and quick sepsis-related organ failure assessment for predicting the need for intensive respiratory or vasopressor support in patients with COVID-19. J Infect 2020.
[6] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052–9.
[7] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020:e200950.
[8] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4):844–7.
[9] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.
[10] Horby PLWSE, J Mafham M, Bell J, Linsell L, Staplin N. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary Report. Med Rxiv 2020.