Letter to the Editor

Giuseppe Lippi*, Brandon Michael Henry, Jonathan Hoehn, Stefanie Benoit and Justin Benoit

Validation of the Corona-Score for rapid identification of SARS-CoV-2 infections in patients seeking emergency department care in the United States

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To the editor,
The diagnosis of coronavirus disease 2019 (COVID-19) is still straightforwardly based on the identification of severe acute respiratory disease coronavirus 2 (SARS-CoV-2) RNA in upper or lower respiratory tracts specimens by means of nucleic acid amplification tests (NAATs) [1]. Nonetheless, these techniques have some important drawbacks, such as the relatively low diagnostic sensitivity in nasopharyngeal swabs (i.e., typically lower than 80%) [2], the need of dedicated instrumentation and specialized personnel, as well as the relatively low throughput, which represent clear obstacles for purposes of large population screening [3].

At least three strategies can be envisaged for improving the efficacy of NAATs and enhancing the throughput of SARS-CoV-2 testing, thus encompassing the use of kits that do not require RNA extraction and purification, the analysis of pools generated from a variable number of clinical specimens, along with the assessment of probability of clinical positivity [4]. The last of these approaches is typically based on the integration of predictive demographic, clinical, and diagnostic parameters, which would then enable the calculation of the likelihood that one subject would have positive NAAT for SARS-CoV-2. One of the first and perhaps most widely used model, the "Corona-Score", incorporates age, sex, presence of infiltrate at chest X-ray, along with values of five laboratory tests: C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and neutrophil and lymphocyte counts [5]. The recent publication of a real-world experience utilizing the Corona-Score in The Netherlands demonstrated 91% accuracy, 96% sensitivity, and 95% specificity for discriminating patients testing positive or negative for SARS-CoV-2 by NAAT upon Emergency Department (ED) admission [5]. Although these data are encouraging, the performance of the model needs to be evaluated in other clinical and healthcare settings, on other categories of patients, and using different analytical methods and instrumentation. Therefore, the purpose of our study was to validate the performance of Corona-Score in a population of US patients seeking ED care for suspected SARS-CoV-2 infection.

The study population consisted of 70 consecutive adults (mean age, 53.5 ± 16 years; 25 women and 45 men), evaluated in the emergency department of the University of Cincinnati Medical Center (UCMC) for suspected COVID-19 and had clinically indicated blood draw. All subjects were prospectively enrolled via Institutional Review Board-approved waiver of informed consent, and research blood samples were collected during EDs visit in April and May 2020. The diagnosis of SARS-CoV-2 infection was confirmed with a positive reverse-transcription polymerase chain reaction (RT-PCR) test on a standard-of-care nasopharyngeal swab. COVID-19 positive patients were stratified into groups based on severity at presentation via their disposition from the ED, as discharged to be treated as outpatient (mild), hospitalized but not needing intensive care (moderate), and needing intensive care (severe).

***Corresponding author: Prof. Giuseppe Lippi**, Section of Clinical Biochemistry, University Hospital of Verona, Piazzale L.A. Scuro, 10, 37134 Verona, Italy, Phone: 0039-045-8122970, Fax: 0039-045-8124308, E-mail: giuseppe.lippi@univr.it
Brandon Michael Henry, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
Jonathan Hoehn and Justin Benoit, Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH, USA
Stefanie Benoit, Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; and Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH, USA

Demographics, cell counts and imaging data were retrieved from the electronic medical record, while CRP, ferritin, and LDH were run directly as research tests. In accordance with the Corona-Score instructions, concentrations of ferritin were multiplied by a harmonization factor of 1.2 for Siemens equipment. Main results were presented as median and interquartile range (IQR). The difference between patient cohorts was assessed using the Mann-Whitney U, Kruskal-Wallis or χ^2 tests, whilst the diagnostic performance of Corona-Score was assessed using receiver operating characteristics (ROC) curve analysis. Statistical analyses were carried out using Analyse-it (Analyse-it Software Ltd, Leeds, UK), with statistical significance set at $p<0.05$.

A total of 44/70 (62.8%) patients were positive for SARS-CoV-2 infection via nasopharyngeal swab RT-PCR testing. The Corona-Score value was found to be significantly higher in patients with SARS-CoV-2 infection (8; IQR, 7–12) compared to those without (5; IQR, 3–7; $p<0.001$). The results of the ROC curve analysis is shown in Figure 1. The area under the curve (AUC) of Corona-Score in our US population of patients seeking ED care was 0.74 (95% CI, 0.61–0.86; $p<0.001$). Using the cut-off values of 4 and 11 originally identified by Kurstjens et al. for their Dutch population [5], the model displayed 82% sensitivity (67% accuracy) and 96% specificity (59% accuracy) in our US population, respectively. Within our cohort of COVID-19 positive patients, the Corona-Score was not observed to increase with worsening disease severity ($p=0.820$) (Figure 2). A specific analysis of the eight NAAT-positive patients with Corona-Score <4 revealed that these were significantly younger (44 ± 16 years vs. 66 ± 14 years; $p=0.036$), were more frequently, though non-significantly, females (63% vs. 34%; $p=0.059$), and especially had a much higher prevalence of non-clinically significant infiltrate at chest X-ray (100% vs. 26%; $p<0.001$).

In conclusion, we found that Corona-Score displays lower AUC (0.74 vs. 0.91) and sensitivity (82% vs. 96%), but slightly higher specificity (96% vs. 95%) in our US cohort of patients seeking ED care compared to a Dutch cohort, which may be at least in part attributable to the different demographic characteristics of our population, the different organization of the national healthcare system and the care access in the US. While it seems unlikely that this scoring system would offer such a high diagnostic accuracy to completely replace NAATs, it may still serve as practical adjunct for adjusting pre- and post-test probabilities. Moreover, it may prove an important tool for screening of sick control groups in COVID-19 clinical studies as noted by Benoit et al. [6]. The lower diagnostic performance in our population can perhaps be explained by the different geographical setting. Circulating strains of the virus were likely different in each region. Moreover, differences in underlying patient co-morbidities may also contribute to these observations. Finally, patients seeking

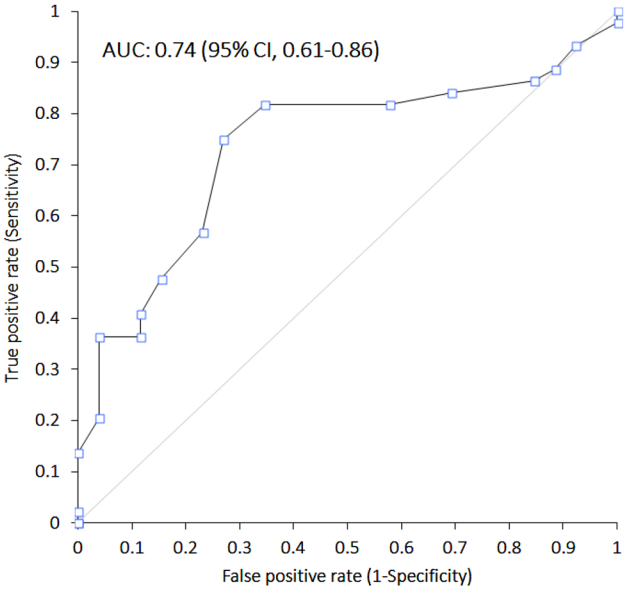

Figure 1: Receiver operating characteristics (ROC) curve analysis of the Corona-Score in a cohort of US patients with suspected coronavirus disease 2019 (COVID-19) seeking emergency department care.

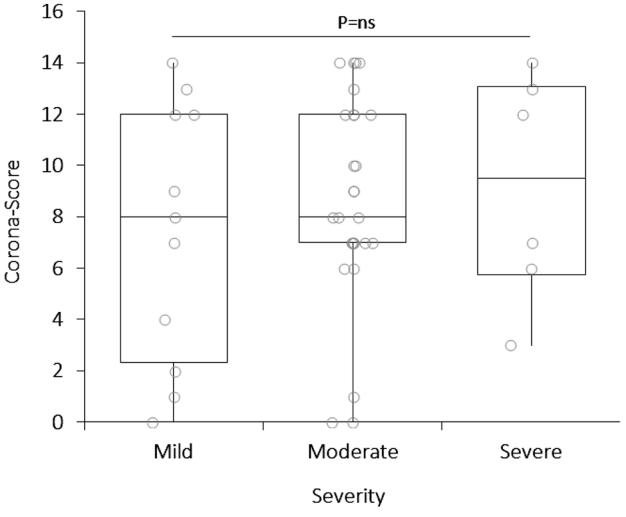

Figure 2: Comparison of Corona-Score values among patients with different degrees of severity of COVID-19.
Mild was defined as outpatient care after emergency department evaluation, moderate was defined as hospitalized but not requiring intensive care, and severe was defined as hospitalized requiring intensive care. *ns–not significant ($p=0.820$).

ED care in the US during the first-wave of the pandemic could have been sicker or presented later than the Europeans, as we observed slightly higher Corona-Score values in our RT-PCR negative patients compared to those calculated by Kurstjens et al. [5] in their validation cohort (i.e., 5 vs. 3). However, as seen in our analysis, COVID-19 severity does not significantly impact the Corona-Score, suggesting that severity may not represent a major source of heterogeneity between the Dutch and US cohorts.

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