Predicting mortality in hospitalized COVID-19 patients

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Prediction of mortality in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection remains an unmet clinical need. An early risk stratification might help in differentiating patients at higher risk of severe disease to provide an adequate care. Several anamnestic, clinical, and blood sample findings were previously reported to associate with a negative outcome, including obesity and metabolic syndrome [1], hypertension [2], inflammatory biomarkers [3], procalcitonin and D-dimer [4], impaired coagulation [5], and even the amount of time spent in the intensive care unit [6]. However, to date none of these emerged above the others. Thus, several mortality risk scores were developed to assist the clinician during the assessment of the patient. Some examples are the Comorbidity, Age, Lymphocyte, and lactate dehydrogenase (CALL) score [7], the modified Nutrition Risk in the Critically ill (mNUTRIC) score [8], the Rapid Emergency Medicine Score (REMS) [9], and the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) Coronavirus Clinical Characterization Consortium (4C) Mortality Score [10].

The CHA2DS2-VASc score was originally designed for assessing the atrial fibrillation stroke risk in non-anticoagulated patients. Together with the HAS-BLED score, CHA2DS2-VASc is used to estimate the thrombotic/hemorrhagic risk in patients requiring thromboprophylaxis such as those with nonvalvular atrial fibrillation [11]. Nonetheless, the CHA2DS2-VASc score was reported to predict mortality in different groups of patients and conditions including subjects with chronic kidney disease [12], after cardiac [13] and noncardiac surgery [14], and acute cerebrovascular events [15]. Recent findings showed that the CHA2DS2-VASc score and its modified forms can differentiate patients at higher risk of worse outcome in course of SARS-CoV-2 infection [16–18]. Our comment concerns the article by Levy et al. in the current issue of Internal and Emergency Medicine that evaluated the role of the modified R₂CHA2DS₂-VASc (M-R₂CHA2DS₂-VASc) score on the prediction of mortality in hospitalized patients with SARS-CoV-2 infection [19].

The M-R₂CHA2DS2-VASc score used by Levy et al. in their current work consists in the adjunction of renal disease, via the evaluation of the estimated glomerular filtration rates, and in changing the original sex category points, adding 1 point to male instead of female gender, to the original CHA2DS2-VASc score. The main outcome of the study was the 30-day mortality. The authors report a positive association between categorized M-R₂CHA2DS₂-VASc score and mortality in coronavirus disease 2019 (COVID-19) patients (30-day mortality rate was 7% for low, 17% for intermediate, and 31% for high M-R₂CHA2DS₂-VASc score group). The enrolled cohort consisted of 800 patients that were hospitalized in a single center in Israel during the first wave of COVID-19 pandemic. The patients were adequately balanced between gender (55.5% were male), with a mean age of 65.2 ± 17 years. Patients with higher M-R₂CHA2DS₂-VASc score were typically older and had more comorbidities, also they more likely required mechanical ventilation support. Of interest, the combination of M-R₂CHA2DS₂-VASc score along with COVID-19 severity categories increased the predictive value of the score alone. Accordingly, in cases of highest M-R₂CHA2DS₂-VASc score and critical COVID-19 infection, the mortality risk reached the 100% (p < 0.01). Furthermore, the authors showed that the M-R₂CHA2DS₂-VASc score was superior to the R₂CHA2DS₂-VASc score in predicting 30 days mortality, as reported in a dedicated ROC curve (AUC: 0.714 and 0.687, respectively; p < 0.01). Figure 1 summarizes main findings.

Such findings confirm the data of previous studies showing the predictive ability against COVID-19-related mortality of the CHA2DS2-VASc score [17, 18], the modified CHA2DS2-VASc score (with male gender = 1 point instead of female) [16, 18, 20], or the R₂CHA2DS₂-VASc score.
considering the renal function [21]. The explanation of such associations should consider the fact that several elements mingle together in determining COVID-19 outcome, most of them included in the score. Indeed, pre-existing comorbidities not only can favor the development of the SARS-CoV-2 infection but they also associate with a worse outcome due to the increased vulnerability of the patient.

Similarly, the infection itself is frequently detected in patients that seek for medical aid because of a different health problem, such as myocardial infarction or acute cerebral events. While a higher number of comorbidities concurs in favoring more serious form of COVID-19 infection, increasing the risk of SARS-CoV-2-related mortality, on the other hand, the COVID-19 infection might be concomitant but not the major cause of death. Several studies investigated the topic of “death for Covid-19” (i.e., main causal role) or “death with Covid-19” (i.e., concurrent, but not critical factor increasing the death risk) and to date SARS-CoV2 is considered a major direct cause of death [22]. Under this point of view, higher M-R2CHA2DS2-VASc scores identify patients with more comorbidities. Accordingly, the Charlson comorbidity index has been proposed as a predictor of mortality in hospitalized patients with SARS-CoV-2 infection [23]. This score was originally developed to identify patients at higher risk of death because of their concomitant diseases. However, while the Charlson comorbidity index considers up to 16 diseases, the M-R2CHA2DS2-VASc is more circumscribed, possibly indicating that few, specific conditions might impact on the SARS-CoV-2 mortality more than others.

Also, elderly patients are known to be more vulnerable to several infectious diseases including COVID-19. Age is considered as one of the most important risk factors for SARS-CoV-2 infection [24]. To guide such an association, the process of aging deeply impacts the host defense ability of the immune system (i.e. immunosenescence), with health issues that goes beyond the mere acute phase of the infection [25]. Concerning sex differences, epidemiological data show that male subjects are more likely to suffer from more severe form of COVID-19, with a higher risk of mortality [26, 27]. As extensively demonstrated, the immune response against pathogens greatly differs among the sexes. With references to SARS-CoV-2 male subjects showed lower circulating levels of IgG antibodies as compared with female [28]. Furthermore, in cases of renal insufficiency, patients have a higher risk of dying [29, 30] probably because the kidney plays a non-negligible role in course of COVID-19-related septic state, as it happens in other forms of sepsis [31]. Furthermore, COVID-19 can directly infect the renal tubules exacerbating the kidney failure [32]. Also, the use of mechanical ventilation concurs in the development of acute kidney injury [33]. As far as hypertension is concerned, the possible higher prevalence in patients with hypertensive state has been pointed out since the very early phases of COVID-19 pandemic. The angiotensin-converting enzyme 2 is recognized as the functional host receptor of the novel coronavirus [34]. From this perspective, speculations were made concerning the possible higher prevalence of the infection in patients treated with angiotensin-converting enzyme inhibitors, but to date the evidence remain scarce. Yet, both a hypertensive state and low blood pressure are associated with a higher mortality in hospitalized COVID-19 patients [35]. In the clinical setting, patients with lowest blood pressure include those directed toward a septic shock; conversely, those with a hypertensive state are frequently dysmetabolic, more inflamed, and with more comorbidities.

Fig. 1 M-R2CHA2DS2-VASc predicts mortality in COVID-19 patients. Summary of the main results by Levy et al.
Also, SARS-CoV-2 infection is associated with neuropathology [36]. Not only the infection itself is related to acute cerebral events [37] but also patients with acute stroke and COVID-19 infection have a worst prognosis [38]. The presence of an inflammatory-hypercoagulability state, together with vessel damages and blood stasis—i.e., the so-called Virchow triad—is associated with a higher risk of thrombus formation. COVID-19 infection is well-known for being associated with vessel alterations and thromboembolism [39]. Not to mention the role of two major chronic diseases such as heart failure and diabetes mellitus, both associated with worse COVID-19 outcome [40–42].

The results of this project confirm the easily accessible CHA₂DS₂-VASc score as a powerful tool able to evaluate the prognosis of patients affected with different comorbidities. Originally created for assessing the risk of stroke in course of atrial fibrillation, this work has preliminary proven its potential in COVID-19 patients. Specifically, adding the renal functionalality and male gender to the score, Levi and coll. have contributed to amplify its capability to detect patients with higher grades of comorbidities and have proven a higher predictive accuracy compared with the R₂-CHA₂DS₂-VASc score. Clinically, COVID-19 ranges from silent forms to severe conditions threatening patients’ life. An early identification of patients prone to develop severe forms of COVID-19 would allow to identify those requiring hospitalization and treatment with available pharmacological tools.

Being an observational, retrospective analysis of patients from a single center, the results require confirmation by wider cohorts. Yet, the identification of the potential of M-R₂CHA₂DS₂-VASc score in identifying COVID-19 patients at higher risk of mortality represents an important step toward the validation of such an easy-to-access tool. Also, such study points out the importance of comorbidities in the pathogenesis of COVID-19. Given the fact that patients with mild symptoms are homogeneously distributed among the 3 classes of risk according to M-R₂CHA₂DS₂-VASc, such study seems to suggest that mortality in patients with Sars-CoV-2 is often due to comorbidities rather than the effect of the virus itself.

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Declarations

Conflict of interest Nothing to declare.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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