

Mortality Risk Assessment Using CHA(2)DS(2)-VASc Scores in Patients Hospitalized With Coronavirus Disease 2019 Infection

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Early risk stratification for complications and death related to Coronavirus disease 2019 (COVID-19) infection is needed. Because many patients with COVID-19 who developed acute respiratory distress syndrome have diffuse alveolar inflammatory damage associated with microvessel thrombosis, we aimed to investigate a common clinical tool, the CHA(2)DS(2)-VASc, to aid in the prognostication of outcomes for COVID-19 patients. We analyzed consecutive patients from the multicenter observational CORACLE registry, which contains data of patients hospitalized for COVID-19 infection in 4 regions of Italy, according to data-driven tertiles of CHA(2)DS(2)-VASc score. The primary outcomes were inpatient death and a composite of inpatient death or invasive ventilation. Of 1045 patients in the registry, 864 (82.7%) had data available to calculate CHA(2)DS(2)-VASc score and were included in the analysis. Of these, 167 (19.3%) died, 123 (14.2%) received invasive ventilation, and 249 (28.8%) had the composite outcome. Stratification by CHA(2)DS(2)-VASc tertiles (T1: ≤ 1 ; T2: 2 to 3; T3: ≥ 4) revealed increases in both death (8.1%, 24.3%, 33.3%, respectively; $p < 0.001$) and the composite end point (18.6%, 31.9%, 43.5%, respectively; $p < 0.001$). The odds ratios for mortality and the composite end point for T2 patients versus T1 CHA(2)DS(2)-VASc score were 3.62 (95% CI: 2.29 to 5.73, $p < 0.001$) and 2.04 (95% CI: 1.42 to 2.93, $p < 0.001$), respectively. Similarly, the odds ratios for mortality and the composite end point for T3 patients versus T1 were 5.65 (95% CI: 3.54 to 9.01, $p < 0.001$) and 3.36 (95% CI: 2.30 to 4.90, $p < 0.001$), respectively. In conclusion, among Italian patients hospitalized for COVID-19 infection, the CHA(2)DS(2)-VASc risk score for thromboembolic events enhanced the ability to achieve risk stratification for complications and death. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;00:1–7)

Coronavirus disease 2019 (COVID-19) is a viral infection causing acute respiratory distress syndrome (ARDS) and was initially observed in December 2019 in Wuhan,

China.¹ One of the concerning features of COVID-19 patients is the development of severe coagulopathy. Indeed, a recent report from Wuhan revealed that among patients

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The study design and data collection are taken by the Italian registry CORACLE including patients of north Italian regions and being and observational Trial it does not require financial resources.

See page 6 for disclosure information.

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who died from COVID-19, 71.4% met criteria for disseminated intravascular coagulation. Some researchers argue that thrombotic derangement is related to multiorgan damage disease or that it is a direct effect of infection on hepatic function. Accordingly, recent studies found a high incidence (25%) of venous thromboembolism in COVID-19 patients.^{2,3} Additionally, elevated levels of D-dimer and fibrinogen have been reported in COVID-19 patients, which appear to be associated with negative outcomes.⁴ Further, others have demonstrated that COVID-19 patients treated with tissue plasminogen activator and heparin experienced more favorable outcomes compared to untreated patients, had improvements in respiratory compliance (expressed by PaO₂/FiO₂ ratio), and had reductions in D-dimer serum levels.^{5,6} These findings may support the hypothesis that the disseminated intravascular coagulation was of a thrombotic origin instead of bleeding diathesis or multiorgan damage.² However recent data of COVID-19 patients' autopsies reveal extensive areas of inflammatory infiltration associated with interstitial oedema and thrombotic lesions in microvessels and in some cases, even massive pulmonary embolism.⁷⁻⁹ On the basis of these findings, we sought to investigate thromboembolic risk in COVID-19 patients by utilizing CHA(2)DS(2)-VASc. Specifically, in this case series, we explored the relationship between CHA(2)DS(2)-VASc score and the need for mechanical ventilation and/or inpatient mortality.

Methods

We used the CORACLE registry, which include relevant data on COVID-19 patients hospitalized in 4 regions of Italy, to perform this analysis. All patients were at least 18 years old, were admitted to the hospital on or after February 22, 2020, and had COVID-19 infection, confirmed using nose or throat swab testing with real-time reverse transcription polymerase chain reaction. All patients received at least 2 venous administrations of low molecular weight heparin as thromboembolism prophylaxis. We chose to restrict this analysis to patients having data available on admission to calculate CHA(2)DS(2)-VASc score, as well as having a known inpatient mortality status (i.e., discharged alive or died in the hospital) at the time of analysis. At hospital admission, all patients gave their written consent to data collection anonymously. The study was conducted according to the principles outlined in the Declaration of Helsinki. This work was approved by the ethical committee of Turin (CORACLE registry: epidemiology clinical characteristics and therapy in real life patients affected by Sars-Cov-2).

The CHA(2)DS(2)-VASc score was calculated as follows: 1 or 2 points in each category as follows: age within 65 to 74 years = 1, age \geq 75 years = 2, female = 1, presence of hypertension = 1, presence of diabetes = 1, previous myocardial infarct or peripheral artery disease = 1, previous stroke = 2, diagnosis of congestive heart failure (HF) = 1. Hence, CHA(2)DS(2)-VASc scores range from 0 to 9 points and a score \geq 2 is associated with thromboembolic risk, indicating the need for anticoagulation in atrial fibrillation patients.¹⁰ We analyzed patients according to data-driven tertiles of CHA(2)DS(2)-VASc scores.

Age and CHA(2)DS(2)-VASc scores were skewed and are presented as median [25th percentile to 75th percentile]. In order to more clearly evaluate risk, we categorized CHA(2)DS(2)-VASc according to data-driven tertiles. Categorical variables are reported as counts and proportions. Differences in patient characteristics across CHA(2)DS(2)-VASc tertiles were assessed via the Kruskal-Wallis Test and Chi-Square test, as appropriate. Receiver operating characteristic (ROC) curve analysis was employed to quantify the prognostic power of CHA(2)DS(2)-VASc score for death and also for the composite end point (death and/or receiving invasive ventilation). We additionally examined crude odds ratios (OR) for death for individual CHA(2)DS(2)-VASc components: age category, gender, hypertension, diabetes mellitus, ischemic heart disease, stroke, and HF. Analyses were performed using SPSS version 20.0.

Results

We collected data from 1045 patients in the CORACLE registry. Of these patients, 864 (82.7%) had data required to calculate CHA(2)DS(2)-VASc score and were included in this analysis. Our sample had a median age of 65 [53 to 76] years and a median CHA(2)DS(2)-VASc score of 2 [1 to 3]. Males were more prevalent than females (62.2%). The rates of comorbidities were as follows: hypertension 48.6%, diabetes 15.7%, ischemic heart disease 11.2%, chronic obstructive pulmonary disease 9.4%, stroke 7.6% and HF 6.1%. Data-driven tertiles of CHA(2)DS(2)-VASc scores were as follows T1: \leq 1, T2: 2 to 3, T3: \geq 4. Patient characteristics according to CHA(2)DS(2)-VASc tertiles are shown in [Table 1](#).

A total of 167 patients (19.3%) died and 123 (14.2%) received invasive ventilation. There were 41 (33.3%) of the ventilated patients who died, whereas 126 (17%) of the 741 nonventilated patients died. The composite outcome of death and/or receiving invasive ventilation was observed in 249 (28.8%) patients. We observed a statistically significant increasing percentage of death (8.1%, 24.3%, 33.3%, respectively; $p < 0.001$) and composite end point (18.6%, 31.9%, 43.5%, respectively; $p < 0.001$) according to tertiles ([Figure 1](#)). The ORs for mortality and the composite end point for patients with the second versus first tertile of CHA(2)DS(2)-VASc score were 3.62 (95% CI: 2.29 to 5.73, $p < 0.001$) and 2.04 (95% CI: 1.42 to 2.93, $p < 0.001$), respectively. Similarly, the ORs for mortality and the composite end point for patients with the third versus first tertile were 5.65 (95% CI: 3.54 to 9.01, $p < 0.001$) and 3.36 (95% CI: 2.30 to 4.90, $p < 0.001$), respectively. ROC curve analysis confirmed that CHA(2)DS(2)-VASc was significantly able to prognosticate both mortality (area under the ROC curve [AUC] = 0.69, 95% CI: 0.65 to 0.73, $p < 0.001$) and the composite end point (AUC = 0.64, 95% CI: 0.60 to 0.68, $p < 0.001$) ([Figure 2](#)).

Moreover, we analysed the crude OR of individual CHA(2)DS(2)-VASc components. Gender did not significantly alter the risk of death (female versus male OR: 0.77, 95% CI: 0.42 to 1.10, $p = 0.145$). Similarly, neither diabetes mellitus (OR: 1.10, 95% CI: 0.70 to 1.73, $p = 0.685$) nor HF (OR: 1.39, 95% CI: 0.72 to 2.66, $p = 0.322$) were significantly associated to mortality. Conversely, age

Table 1

Clinical characteristics of patients hospitalized for COVID-19 infection in the Italian CORACLE registry according to thromboembolic risk quantified by CHA(2)DS(2)-VASc Score

Variable	CHA(2)DS(2)-VASc scores				p value
	All patients (n = 864)	≤1 (n = 381)	2 – 3 (n = 276)	≥4 (n = 207)	
Age (years)	65 [53-76]	53 [45-59]	71 [65-78]	80 [74-85]	<0.001
Men	537 (62.2%)	281 (73.8%)	160 (58%)	96 (46.4%)	<0.001
Hypertension	420 (48.6%)	58 (15.2%)	175 (63.4%)	187 (90.3%)	<0.001
Diabetes mellitus	136 (15.7%)	9 (2.4%)	45 (16.3%)	82 (39.6%)	<0.001
Chronic obstructive pulmonary disease ¹	81 (9.4%)	11 (2.9%)	32 (11.6%)	38 (18.4%)	<0.001
Heart failure	53 (6.1%)	2 (0.5%)	5 (1.8%)	46 (22.2%)	<0.001
Ischemic heart disease/PAD	107 (12.4%)	0	25 (9.15)	82 (39.6%)	<0.001
Stroke	66 (7.6%)	0	11 (4%)	55 (26.6%)	<0.001
Smoker ¹⁶⁷					0.47
Current	65 (9.3%)	23 (7.8%)	22 (9.8%)	20 (11.2%)	
Former	48 (6.9%)	17 (5.8%)	15 (6.7%)	16 (8.9%)	
Chronic Kidney Disease ⁵⁴³	77/321(24%)	18/172(10%)	33/123(27%)	26/103(25%)	<0.001
Atrial Fibrillation ⁴⁶⁴	39/400(9.5%)	5/179(2.8%)	12/140(8.5%)	22/115(19%)	<0.001
Therapy					
ACEi ¹	156 (18.1%)	24 (6.3%)	68 (24.7%)	64 (30.9%)	<0.001
ARB ¹	127 (14.7%)	16 (4.2%)	58 (21.1%)	53 (25.6%)	<0.001
Beta-blockers ¹	168 (19.4%)	20 (5.2%)	60 (21.8%)	88 (42.5%)	<0.001
Calcium channel blockers ¹	152 (17.6%)	22 (5.8%)	70 (25.5%)	60 (29%)	<0.001
Thiazid diuretics ⁴⁹	107 (13.1%)	10 (2.8%)	34 (13.4%)	63 (31.3%)	<0.001
Loop diuretics ²⁶⁸	93 (15.6%)	11 (5.0%)	27 (13.6%)	55 (30.9%)	<0.001
Acetil salicylic acid ¹⁷⁸	105 (15.3%)	11 (3.4%)	41 (19.1%)	53 (34.9%)	<0.001
Peripheral oxygen saturation (%) ⁴⁸⁷	95 [91-97]	96 [94-98]	95 [91-97]	93[89-96]	<0.001
Respiratory rate (n) ⁷¹⁷	26 [19-28]	25 [20-27]	24 [18-30]	27 [20-30]	0.25
D-dimer (ng/ml) ⁶⁹⁰	610	609	609	620	0.90
Troponin (ng/ml) ⁶⁹⁰	[122-1361]	[71-1535]	[181-1078]	[175-1400]	<0.001
	19 [9-51]	11 [7-28]	22 [9-51]	50[13-115]	

ACEi = angiotensin II converting-enzyme inhibitor; ARB = aldosterone receptor blocker; PAD = peripheral artery disease (2.5% of total population).

Continuous variables: median [quartile 1, quartile 3].

Superscripts indicate missing data.

demonstrated a strong association with mortality (65 to 74 vs <65 years OR: 2.45, 95% CI: 1.49 to 4.02, $p < 0.001$; 75 + vs <65 years OR: 6.36, 95% CI: 4.16 to 9.71, $p < 0.001$). Further, hypertension (OR: 2.57, 95% CI: 1.80 to 3.67, $p < 0.001$), stroke (OR: 2.43, 95% CI: 1.42 to 4.16, $p = 0.001$) and ischemic heart disease and/or peripheral artery disease

(OR: 2.42, 95% CI: 1.56 to 3.77, $p < 0.001$) were all significantly associated with death (Figure 3).

Discussion

To our knowledge, this is the first study to stratify COVID-19 patients according to CHA(2)DS(2)-VASc score. Our findings indicate that in this Italian population, patients with higher CHA(2)DS(2)-VASc scores had higher likelihoods of adverse outcomes. Patients with CHA(2)DS(2)-VASc score = 2 to 3 and CHA(2)DS(2)-VASc score ≥ 4 had a higher rate of adverse events in terms of both mortality and the composite end point of invasive ventilation and/or mortality than those with CHA(2)DS(2)-VASc score ≤ 1. ROC curve analysis confirmed the prognostic ability of CHA(2)DS(2)-VASc score. Additionally, individual components of the CHA(2)DS(2)-VASc score, such as age, hypertension, stroke, and ischemic heart disease and/or peripheral artery disease impacted patient outcomes. In this hospitalized sample, approximately 12% presented with severe respiratory distress or sudden oxygen desaturation requiring invasive ventilation and intensive care unit (ICU) admission. Although many clinical variables included in CHA(2)DS(2)-VASc such as age, hypertension, and Cardiovascular (CV) diseases, were demonstrated to increase

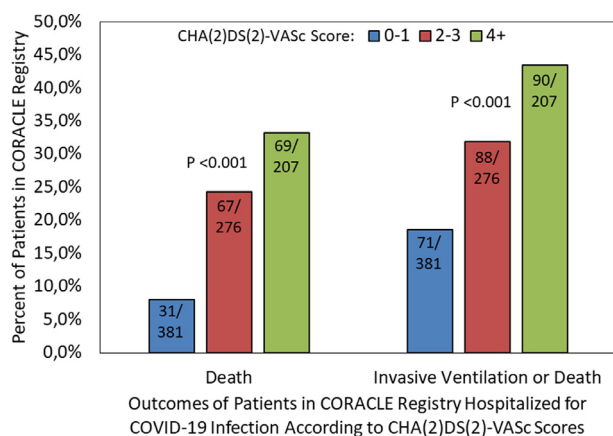


Figure 1. Rates of death and composite end point (death or invasive ventilation) according to tertiles of CHA(2)DS(2)-VASc scores (Differences in adverse events rate across CHA(2)DS(2)-VASc tertiles were assessed via the chi-square test).

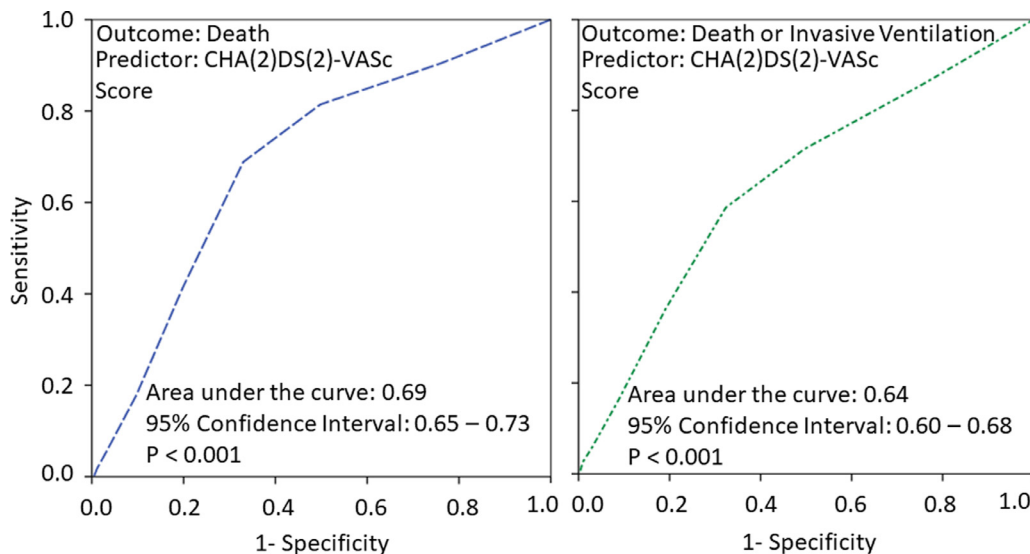


Figure 2. Receiver Operating Characteristic curves for death and the composite end point of death or invasive ventilation for the predictor of CHA(2)DS(2)-VAsC score (ROC curve analysis was employed to quantify the prognostic power of CHA(2)DS(2)-VAsC score for death and also for the composite end point (death and/or receiving invasive ventilation)).

the risk in this setting, until now a precise scale and weight of each variable were lacking. Indeed several studies demonstrated that patients with high CV risk and history of CAD, ictus, HF experienced a worse prognosis. Whereas female gender that is included in CHA(2)DS(2)-VAsC appears to be a protective factor in COVID patients.

The most commonly recognized features characterizing COVID infection are low oxygen saturation and high respiratory rate. Both clinical manifestations are likely suggestive of extensive lung infection diffusion, bilateral involvement, and increased alveolar permeability with severe tissue damage. In

this scenario, patients admitted to the ICU undergoing to non-invasive or invasive mechanic ventilation, often died.¹¹ A John Hopkins hospital report including 1,441,128 COVID-19 cases showed that about 20% of patients need ICU admission with invasive respiratory management. Among severe ARDS cases, alterations in blood-clotting have been observed, with possible microthrombi occurring within the tiny blood vessels interacting with the lung alveoli, preventing capillaries from filling, and leading to impaired gas exchange.¹² Therefore, there is an unmet need for the early recognition of these severe and/or critical patients before ARDS occurs.

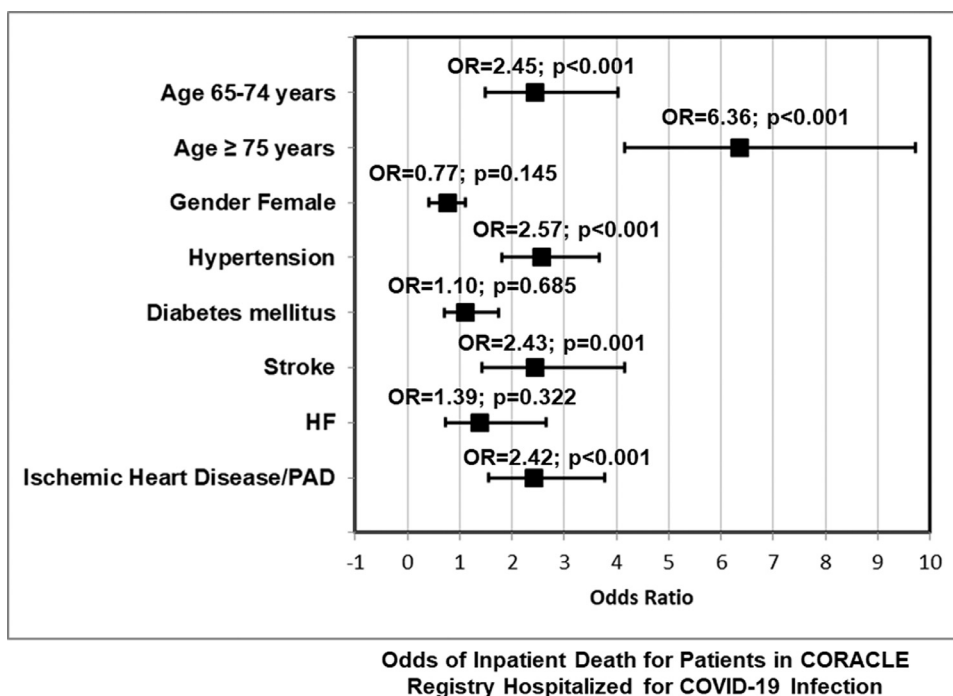


Figure 3. Forest plot of odds ratios for mortality of individual CHA(2)DS(2)-VAsC components (crude OR for death for individual CHA(2)DS(2)-VAsC components: age category, gender, hypertension, diabetes mellitus, ischemic heart disease, stroke, and heart failure).

Notably, others have attempted to build prediction models in order to better risk stratify COVID-19 patients. Two Chinese reports identified the following variables as being related to a poorer prognosis: advanced age, high C-Reactive Protein levels, and large comorbidity burden.¹³ Similarly, a retrospective analysis of 487 patients revealed that older age, male gender, and hypertension were all independent predictors of severe COVID-19 disease requiring hospital admission.¹⁴ Further, a retrospective, multicentre cohort study of 191 Chinese COVID-19 patients demonstrated that older age, higher Sequential Organ Failure Assessment score, and D-dimer $>1 \mu\text{g/ml}$ were independently associated with in-hospital death, revealing significant power to detect high risk subjects.⁴ Similarly, other reports have demonstrated that increased levels of D-dimer and fibrinogen, as well as lower levels of platelets, are indicative of severe infection.^{2,15–18} These findings have prompted the use of tissue plasminogen activator and heparin, which have been associated with decreased COVID-19 disease severity.^{5,6} Other laboratory markers such as PAI-I, platelet counts, interleukins, have been analysed in order to initially identify patients with higher risk of complications. Unfortunately, none of these variables are recognized in most common scores used for thromboembolic events prediction. Our approach using the CHA(2)DS(2)-VASc score has the advantages over these prior attempts of risk stratification in that it is simple, can be done upon admission, and is not dependent on or confounded by laboratory or other measurements. However, we cannot assert that current score may be applicable in all COVID populations presenting with different clinical characteristics, CV risk, and respiratory disease involvement. Accordingly, a larger sample size from the UK showed some discrepancies in terms of baseline risk profile and mortality rate compared to our sample size, and CHA(2)DS(2)-VASc should be tested in a larger population before being systematically applied.¹⁹ However, comparing ventilated patients with those of the cited study, the mortality risk appears quite similar.²⁰ This percentage reflects the mortality rate of the larger Italian analysis of ICU patients in Lombardy (1,591 patients). Indeed, Grasselli et al, reported a 26% mortality rate among ICU patients. Patients who did not receive invasive ventilation may have died due to a contraindication of invasive ventilation, resulting in respiratory deterioration.²¹

It should be biologically plausible that the CHA(2)DS(2)-VASc score would predict outcomes for patients with COVID-19 infection. Some reports demonstrated that sudden clinical deterioration is often linked to increased intravascular coagulation, and several concerns were recently raised regarding the possible relation between COVID-19 infection and blood-clotting alteration.¹¹ However, no data exist regarding the prophylactic use of anticoagulant drugs, although COVID-19 patients are prone to thromboembolic events and DIC.^{2,3,22–24} The mechanisms underlying infection, inflammation and coagulopathy in COVID-19 disease are poorly understood, but likely reflect the course of similar viral infections, such as SARS and ebola.² In normal conditions, the coagulation cascade activation recognizes 3 different pathways: the antithrombin system, the endothelial protein C system, and tissue factor pathway inhibitor.

In acute sepsis, all these pathways are inhibited due to impaired synthesis, ongoing consumption and proteolytic degradation leading to a complete derangement of endothelial function in peripheral vessels and capillary district. Overexpression of tissue factor, activation of C protein system, and the inhibition of physiological fibrinolysis processes represent the key mechanisms involved in this coagulopathy. Indeed, viral infection and subsequent immune response mediated by macrophages and T lymphocytes generate an overexpression of immune mediators such as cytokines and chemokines (interleukin (IL)-1, IL-6, IL-8, IL-21, TNF- β and Monocyte chemoattractant protein-1), which activate endothelium. Therefore, Tumor necrosis factor, IL-6 and IL-1 amplify the procoagulant activity stimulating both thrombi formation and increased vascular permeability due to its endothelial effects.^{25–28} In the lung, excretion of fibrin is related to alveolar damage through hyaline membrane deposition, which lead to alveolar collapse. Together with alveolar collapse, microvascular thrombi impair gas exchange, which results in ARDS and acute lung injury. Although, the CHA(2)DS(2)-VASc is primarily designed for embolic risk prevention in atrial fibrillation, the prothrombotic state related to COVID-19 infection likely involves both micro and macro vascular pulmonary district reflecting diffuse endothelial dysfunction. This procoagulant activity may also be systematically present in several organs, and it could also facilitate the risk of large vessel thrombo-embolic disease.²⁹ Therefore, the clinical scenario includes an initial viral infection of the respiratory tract experiencing the first host immune response. In specific conditions in which inflammation is associated with the cytokine storm and the immune response upregulation, a pro-coagulation state prevails.²⁹

Our study has all the limitations of retrospective studies of prospectively collected data. A detailed laboratory analysis contemporarily investigating D-dimer, fibrinogen, and plasminogen levels was not available for study. Accordingly, a more detailed score including both clinical and laboratory variables deserve a specific analysis and validation and it could become much more appropriate for risk assessment definition in this setting. CHA(2)DS(2)-VASc could reasonably forecast thromboembolic complications, but other CV complications such as acute coronary syndrome, acute HF, myocarditis, and arrhythmic event, could be underestimated. Our population did not include any data regarding baseline physical activity, cardiorespiratory fitness and body mass index. Moreover, this analysis lacks of some data about clinical data, laboratory analysis variables, comorbidities and therapy. Moreover, external validation of our analysis in a separate cohort is required to better understand the model's ability to prognosticate outcomes for COVID-19 patients. Our results have been validated in hospitalized patients in Italy with bed positioning and cannot be generalized to nonhospitalized patients with less severe conditions in other countries. Finally, we do not know whether additional heparin treatment or other anticoagulant drugs could potentially prevent hypercoagulation.

In conclusion, patients hospitalized for COVID-19 infection are at high risk for systemic and pulmonary embolization. We found that in this case series of Italian patients,

those with higher CHA(2)DS(2)-VASc scores had higher rates of mechanical ventilation or death; CHA(2)DS(2)-VASc scores could be easily calculated at admission in order to initially discern patients with increased thromboembolic risk. It is plausible that clinicians may wish to choose a specific anticoagulant treatment for such high risk patients. At present, whether patients hospitalized with COVID-19 with higher CHA(2)DS(2)-VASc scores should be considered for a specific anticoagulant treatment as well as other hypotheses generated by these descriptive data, require direct testing in analytic studies designed a priori to do so.

Authors Contribution

Gaetano Ruocco: Conceptualization, Methodology, Writing- Original draft preparation, Reviewing and Editing. Peter A. McCullough, Kristen M. Tecson: Writing- Original draft preparation, Reviewing and Editing. Massimo Mancone, Gaetano M. De Ferrari, Fabrizio D'Ascenzo, Francesco G. De Rosa: Visualization, Investigation, Reviewing and Editing. Anita Paggi, Giovanni Forleo, Gioel G. Secco, Gianfranco Pistis, Silvia Monticone, Marco Vicenzi, Irene Rota, Francesco Blasi, Francesco Pugliese: Visualization, Investigation. Francesco Fedele: Visualization, Investigation, Reviewing and Editing. Alberto Palazzuoli: Conceptualization, Methodology, Writing- Original draft preparation, Reviewing and Editing.

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Disclosures

The authors have no conflicts of interest to disclose.

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