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Original Article

Risk prediction of major cardiac adverse events and all-cause death following covid-19 hospitalization at one year follow-up: The HOPE-2 score☆

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ABSTRACT

Background: Long-term consequences of COVID-19 are still partly known.
Aim of the study: To derive a clinical score for risk prediction of long-term major cardiac adverse events (MACE) and all cause death in COVID-19 hospitalized patients.
Methods: 2573 consecutive patients were enrolled in a multicenter, international registry (HOPE-2) from January 2020 to April 2021 and identified as the derivation cohort. Five hundred and twenty-six patients from the Cardio-Covid-Italy registry were considered as external validation cohort. A long-term prognostic risk score for MACE and all cause death was derived from a multivariable regression model.
Results: Out of 2573 patients enrolled in the HOPE-2 registry, 1481 (58 %) were male, with mean age of 60±16 years. At long-term follow-up, the overall rate of patients affected by MACE and/or all cause death was 7.8 %. After multivariable regression analysis, independent predictors of MACE and all cause death were identified. The HOPE-2 prognostic score was therefore calculated by giving: 1–4 points for age class (<65 years, 65–74, 75–84, ≥85), 3 points for history of cardiovascular disease, 1 point for hypertension, 3 points for increased troponin serum levels at admission and 2 points for acute renal failure during hospitalization. Score accuracy at ROC curve analysis was 0.79 (0.74 at external validation).

☆ The manuscript: 1) the paper is not under consideration elsewhere2) none of the paper's contents have been previously published3) all authors have read and approved the manuscript.

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Stratification into 3 risk groups (<3, 3–6, >6 points) classified patients into low, intermediate and high risk. The observed MACE and all-cause death rates were 1.9 %, 9.4 % and 26.3 % for low- intermediate and high-risk patients, respectively (Log-rank test $p < 0.01$).
Conclusions: The HOPE-2 prognostic score may be useful for long-term risk stratification in patients with previous COVID-19 hospitalization. High-risk patients may require a strict follow-up.

1. Introduction

COVID-19 is an infectious disease that has become pandemic from 2020. Data on acute outcome, showed that among hospitalized patients mortality rates were 15.8 % in USA[1] and 22 % in Europe [2,3]. Long term consequences of COVID have been described as persistence of COVID-19 symptoms beyond 3 months and named as Long-COVID [4]. Cardiac symptoms as shortness of breath, chest pain, fatigue, and postural orthostatic tachycardia have been described [5]. Moreover, several cardiovascular (CV) diseases have been reported after the acute phase including myocardial inflammation, myocardial and brain infarction, and venous thrombosis [6].

Xie et al., evaluating national USA health care database, found an increased burden of cardiovascular outcomes after COVID-19 infection at 12 months. An increased burden was found mostly in hospitalized patients, with higher prevalence among intensive care unit patients [7]. However, also non-hospitalized patients may show signs of subclinical multi-organ affection involving cardiac, pulmonary and renal function [8].

Possible predictors of cardiovascular long-term events after COVID-19 hospitalization have been identified in several studies. Renda et al. found in a cohort of 296 patients that female sex, in-hospital acute heart failure during index hospitalization and atrial fibrillation significantly predicted the incident risk of long-term MACE [9]. Ortega-Paz et al. in a multicenter registry of 4427 patients showed that predictors of adverse CV events were history of valvular heart disease, atrial fibrillation, heart failure, active or previous cancer, smoke and hypertension [10].

However, clinical score for possible predictors of cardiovascular long-term events after COVID-19 hospitalization are poorly identified and the ASCVD (atherosclerotic cardiovascular disease) risk score failed to predict long-term MACE in a large cohort of US Veterans[11].

Aim of this study was therefore to derive a simple clinical score for risk prediction of long-term major adverse cardiovascular events (MACE) and all-cause death among patients with previous hospitalization for COVID-19 infection.

2. Methods

The present study involved a cohort of 2573 patients from the HOPE 2 COVID-19 registry. The HOPE-2 registry is a multicenter international registry which included patients from nine countries: Spain, Italy, Germany, Serbia, China, United States of America, Canada, Cuba and Ecuador (NCT04778020). Mean follow-up time was 327 ± 102 days.

The protocol was established by a scientific board from Italy, Spain, Ecuador, Germany and United States. Detailed information about participating hospitals, investigators, collaborators and the protocol have been previously published [12]. All patients were diagnosed with COVID-19 according to World Health Organization (WHO) interim guidance, through polymerase chain reaction (PCR) testing. In this analysis, hospital data and patients were included from 16th January 2020 until 30th April 2021. Follow-up was closed on the 31st December 2021.

This study was approved by the local ethics committee and was consistent with the guidelines of Helsinki. All local principal investigators reviewed the draft and checked for the accuracy and veracity of data.

2.1. Data extraction

Epidemiological, clinical, and in-hospital outcome data were manually extracted from electronic medical records and evaluated by medical researchers. Each definition of clinical outcomes was recorded and checked by at least two medical doctors in each hospital. Patient's data were anonymized, and the electronic data were stored and/or filled in an encrypted, password-protected computer/website. All cause death (including cardiovascular and non cardiovascular mortality) and long-term MACEs were verified by outpatient visits, medical records, or phone interviews. Only patients with available follow-up of at-least 6 months were included.

Throat swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase–PCR assays according to the WHO recommendation. Additionally, patient's clinical and laboratory data and imaging test were extracted. Respiratory insufficiency was defined as inadequate gas exchange by the respiratory system associated with increased respiratory rate, abnormal blood gases (hypoxemia, hypercapnia, or both), and evidence of increased work of breathing [13].

Admission troponin serum levels (including high sensitivity troponin, either troponin T or troponin I) greater than the 99th percentile of normal values, as per manufacturer indications were recorded as increased troponin levels. Acute renal failure was defined as Creatinine serum levels 3 times higher than admission values or increase to ≥4·0 mg/dL or acute dialysis, or urine volume <0·3 mL/kg for ≥24 h [14].

History of cardiovascular disease included coronary artery disease, heart failure, cardiac arrhythmias and valvular disease. Hypertension was defined according to ESC/ESH guidelines [15]. Sepsis was defined as surviving sepsis campaign – COVID-19 guidelines [16]. Additional information on data records have been provided in previous articles from this research group [17–19].

3. Study outcome

We considered as primary outcome MACE at long-term follow-up and all cause-death, only after hospital discharge. MACE included acute myocardial infarction, stroke, heart failure hospitalization, cardiac arrhythmias requiring hospitalization, and venous thrombosis (DVT)). Events were allocated following Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) [16].

3.1. Statistical analysis

Continuous variables were expressed as mean (SD) and compared with a *t*-test or Mann-Whitney test as required. Categorical variables were presented as percentages and compared with a χ^2 or Fisher test as required. The Kolmogorov-Smirnov test was used to identify variables with normal distribution. Linear regression was assessed with a Pearson test. Logistic regression analysis was used to estimate the risk of all cause death and MACE associated with clinical variables; odds ratio (ORs) and 95 % confidence intervals (CIs) were also calculated.

First, variables significantly associated with all cause death and MACE at univariable regression analysis were further examined in a multivariable regression analysis. Regression coefficients of the variables statistically significant at multivariable analysis were therefore used to estimate a clinical score for the prediction of all cause death and MACE. The "weight" of each variable significant at multivariable

regression analysis and included in the score was derived as multiple of the smaller significant regression coefficient. Three categories of risk (low, intermediate, and high) based on this score were identified and compared in a Cox regression model. Hazard ratios (HR) with 95 % CIs were estimated. The accuracy of the score was assessed with receiver operating characteristic (ROC) curves analysis and validated in an adjunctive population of patients from the Cardio-Covid-Italy multicenter registry [20,21].

The final model was tested for goodness of fit using the Hosmer–Lemeshow statistic. A p-value <0.05 (2-tailed) was considered statistically significant.

4. Results

Among 2573 patients enrolled in the HOPE-2 registry, 1481 (58 %) patients were male; mean age was 60 ± 16 years. Baseline population features are summarized in Table 1.

Two hundred and two out of 2573 (7.8 %) patients died or experienced MACE at long term (1.5 % cardiovascular death, 2.3 % non cardiovascular death, 1.3 % acute coronary syndrome, 1.2 % heart failure, 0.9 % cardiac arrhythmias, 0.8 % venous thrombosis and 0.7 % acute cerebrovascular accident). These patients were older (69 ± 13 vs 59 ± 17, $p < 0.01$), had higher prevalence of hypertension (83 vs 42 %, $p < 0.01$), diabetes (22 vs 11 %, $p < 0.01$) and history of heart disease (68 vs 14 %, $p < 0.01$) (Table 1).

During hospitalization these patients experienced more frequently heart failure (17 vs 4 %, $p < 0.01$), respiratory insufficiency (48 vs 37 %, $p < 0.01$), and acute renal failure (8 vs 4 %, $p = 0.02$).

Table 1
Baseline features of general population.

	Overall derivation cohort	MACE +All cause death	No MACE No death	p-value
		Mean ± S.D.	Mean ± S.D.	
N. patients	2573	202	2371	
Age, y	60 ± 16	69 ± 13	59 ± 17	**<0.01**
Male sex	58 %	63 %	57 %	0.11
Baseline clinical profile				
Hypertension	45 %	83 %	42 %	**<0.01**
Diabetes	15 %	22 %	11 %	**<0.01**
Obesity (BMI > 30)	18 %	23 %	17 %	0.06
History of lung disease	15 %	17 %	14 %	0.25
History of heart disease	19 %	68 %	14 %	**<0.01**
History of cancer	10 %	14 %	11 %	0.05
Clinical features during hospitalization				
Heart failure	5 %	17 %	4 %	**<0.01**
Respiratory insufficiency	38 %	48 %	37 %	**<0.01**
Acute renal failure	4 %	8 %	4 %	**0.02**
Admission Glasgow coma score	14.8 ± 0.9	14.4 ± 2.1	15 ± 0.7	**<0.01**
Sepsis	6 %	19 %	5 %	**<0.01**
Laboratory data during hospitalization				
Procalcitonin > ULN	11 %	18 %	10 %	**<0.01**
PCR > ULN	75 %	79 %	75 %	**0.01**
Troponin > ULN	10 %	35 %	8 %	**<0.01**
D-Dimer > ULN	51 %	55 %	51 %	0.07
Hemoglobin (g/L)	13 ± 1.8	12.5 ± 1.2	13.2 ± 1.2	**<0.01**
Admission creatinine levels (mg/dl)	1.16 ± ± 0.9	1.44 ± ± 1.04	1.13 ± ± 0.9	**<0.01**
Admission Platelets ($x10^9$/L)	222 ± 95	213 ± 107	223 ± 94	**<0.01**
Long term adverse events				
Bleeding	0.8 %	5 %	0.5 %	**<0.01**
Non cardiovascular hospital admission	11 %	31 %	9 %	**<0.01**
Death	3.8 %	37 %	0 %	<0.01

Legend: BMI = body mass index, MACE = major cardiovascular event, ULN = upper limit of normal.

5. The HOPE-2 prognostic score

Among these features, the following variables, also available in the validation cohort, were identified as possible independent predictors of MACE and all-cause death at multivariable logistic regression analysis: age (OR 1.384, 95 % CI 1.191–1.608, $p < 0.001$), hypertension (OR 1.831, 95 % CI 1.243–2.968, $p = 0.002$), history of cardiovascular disease (OR 2.730, 95 % CI 1.938–3.846, $p < 0.001$), and increased troponin serum levels at admission (OR 2.855, 95 % CI 1.944–2.194, $p < 0.001$) (Table 2).

According to the coefficients in multivariable regression analysis, the HOPE-2 prognosis score was derived by attributing 1–4 points for age class (<65y, 65–74y, 75–84y, ≥85y), 3 points for history of cardiovascular disease, 1 point for hypertension, 3 points for increased troponin serum levels at admission and 2 points for acute renal failure during hospitalization (Fig. 1). Score accuracy at ROC curve analysis (AUC) was 0.79 (95 % CI 0.76–0.82, $p < 0.001$). (**Suppl. Figure 1**). The goodness of fit using the Hosmer-Lemeshow statistic was not statistically significant.

Stratification into 3 risk groups (score <3, score between 3 and 6, and score >6 points) classified 1333 (52 %) as having low risk, 883 (34 %) as having intermediate risk, and 357 of 2573 patients (14 %) as having a higher risk of long-term MACE and all cause death. The observed MACE and all cause death occurrences at follow-up were 1.9 % (25 of 1333) for low-risk patients, 9.4 % (83 of 883) for intermediate-risk patients, and 26.3 % (94 of 357) for high-risk patients (Fig. 2). MACE and all cause death free survival was significantly different according to risk score stratification (Log-rank p-value<0.01, Fig. 3). In the Cox regression analysis, the hazard ratio associated with intermediate HOPE-2 risk class (vs low risk class) was 5.49 (95 % CI 3.51–8.59, $p < 0.01$, sensitivity 88 %, specificity 55 %, positive predictive power 14 %, negative predictive power 98 %), while the hazard ratio associated

Table 2
Univariate and multivariate logistic regression analysis of predictors of major cardiac adverse events (MACE) and all-cause death, odds ratios and 95 % confidence intervals.

Variable	Univariable			Multivariable		
	OR	95 % CI	p-value	OR	95 % CI	p-value
Gender	1.086	0.81–1.45	0.58			
Age	1.04	1.03–1.05	<0.01	1.38	1.19–1.60	<0.01
Hypertension	4.40	3.14–6.15	<0.01	1.83	1.24–2.96	0.02
Diabetes	1.90	1.34–2.68	<0.01			
History of renal failure	3.08	1.86–5.08	<0.01			
History of heart disease	5.59	4.15–7.53	<0.01	2.73	1.93–3.84	<0.01
Admission troponin levels >ULN	4.97	3.57–6.92	<0.01	2.85	1.94–2.19	<0.01
Respiratory insufficiency at admission	1.70	1.27–2–26	<0.01			
In hospital heart failure	5.31	3.48–8.09	<0.01			
Acute renal failure	3.45	2.36–5.03	<0.01	1.48	0.94–2.33	0.08
In-hospital bleeding	4.55	2.47–8.38	<0.01			
In-hospital thrombo-embolic events	1.98	0.82–4.77	0.12			

Legend: ULN = upper limit of normal.

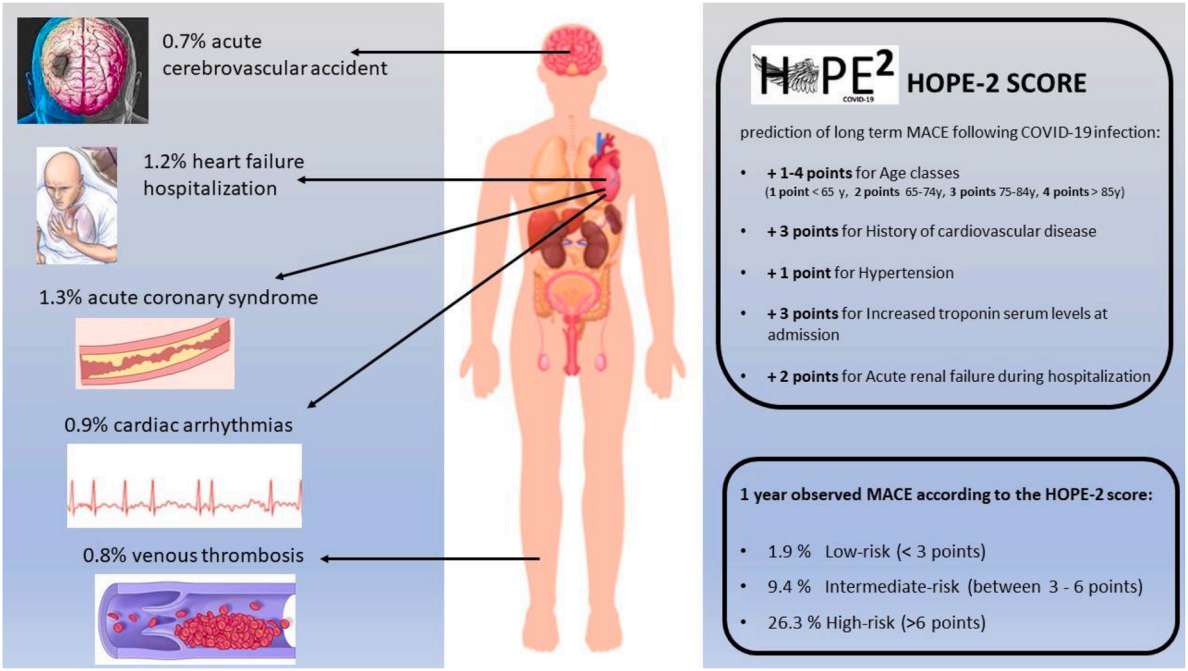


Fig. 1. Rate of Major cardiac adverse events at one year follow-up after COVID-19 hospitalization and clinical features to evaluate for a long-term risk stratification with the HOPE-2 score.

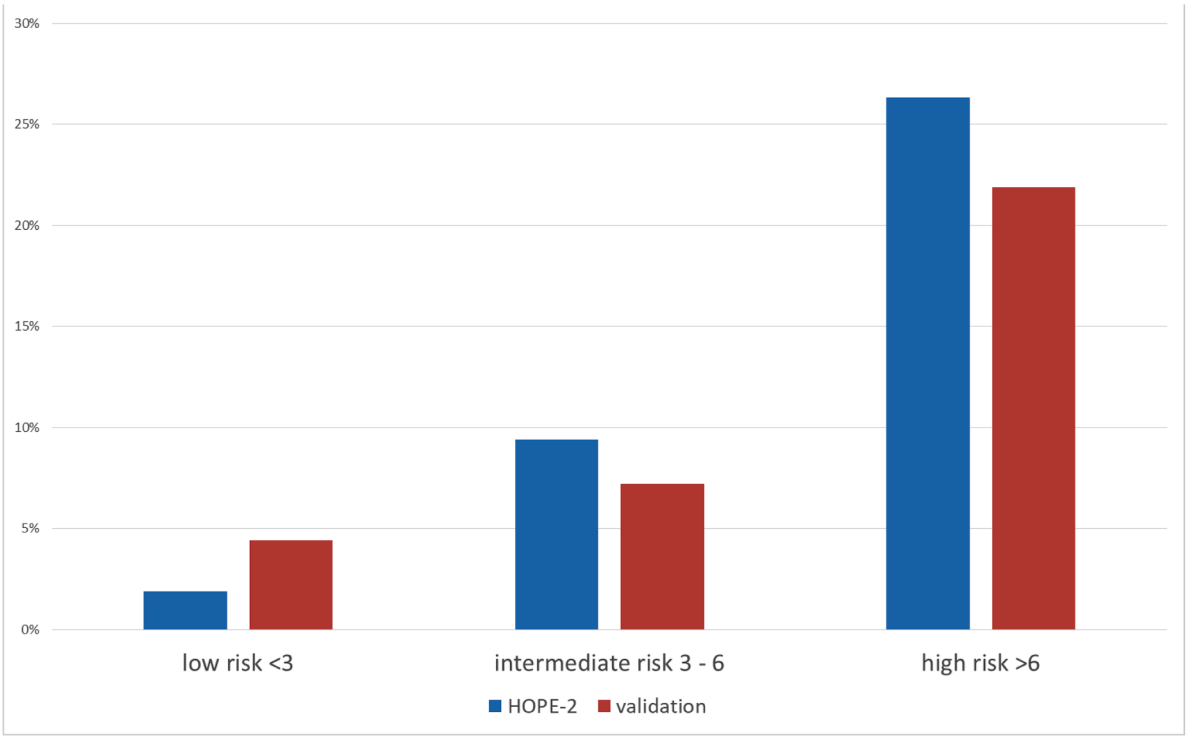
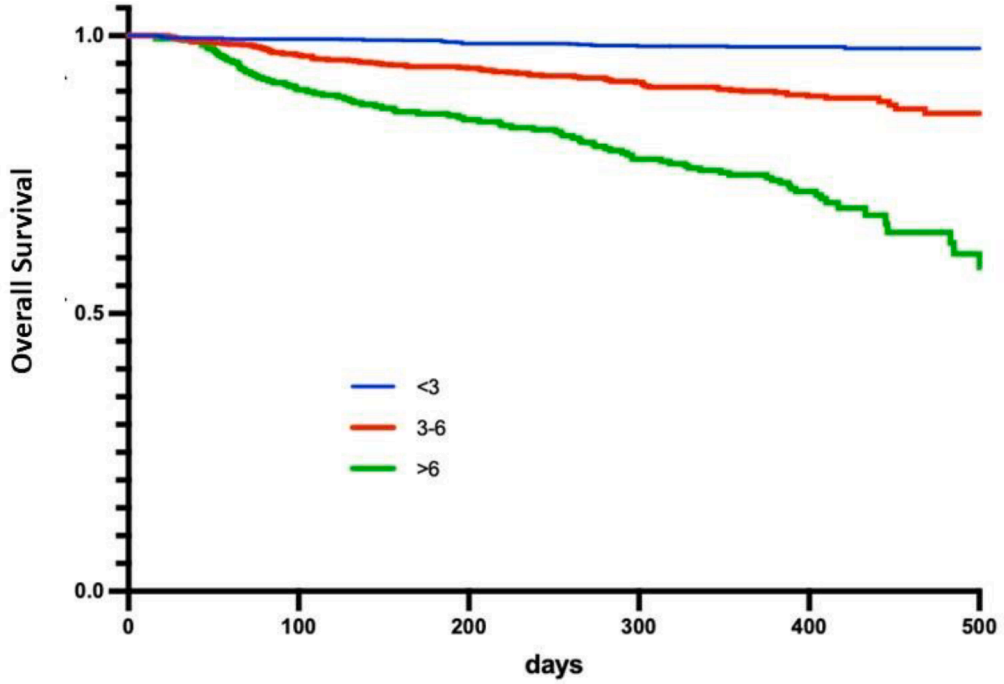


Fig. 2. Observed long-term major adverse cardiovascular events (MACE) and all-cause death according to risk score stratification in the HOPE-2 registry and in the Cardio-Covid-Italy registry (validation cohort).
Legend: score ⟨ 3 points = low risk patients, score between 3 and 6 points = intermediate risk patients, score ⟩ 6 points = high risk patients.

with high HOPE-2 risk class (vs low risk class) was 16.53 (95 % CI 10.62–25.62, $p < 0.01$, sensitivity 47 %, specificity 89 %, positive predictive power 26 %, negative predictive power 95 %).

6. Validation of the HOPE-2 prognostic score

Among the 526 patients from the external validation cohort (**Suppl. Table 1**), only 453 had complete data on the variables of interest and were used to validate the score. Among them, 35 % (159 of 453) were in the low-risk group 37 % (166) in the intermediate-risk group, and 28 %



number at risk

< 3	1286	1166	1018	825	412	57
3 - 6	827	696	594	459	218	34
> 6	336	269	230	169	79	14

Fig. 3. Kaplan Meier curve of overall survival from major adverse cardiac events (MACE) and all-cause death among patients enrolled in the HOPE-2 registry according to the risk groups of the score (Log-rank p-value<0.01). Legend: < 3 points = low risk patients, 3–6 points intermediate risk patients, > 6 points high risk patients.

(128) in the high-risk group. Long-term MACE and all cause death rates were 4.4 % (7 of 159) in the low-risk group, 7.2 % (12 of 166) in the intermediate-risk group, and 21.8 % (28 of 128) in the high-risk group ($p < 0.001$) (Fig. 2). Rates of cardiovascular and non cardiovascular mortality in each group were as follows: 0.5 % and 1.6 % in the low-risk group, 1.7 % and 2.1 % in the intermediate-risk group and 1.5 % in the high-risk group.

The ROC curve analysis revealed a good discrimination of the HOPE-2 score even in the validation cohort, with an AUC of 0.74 (95 % CI, 0.657–0.819, $p < 0.01$, p n.s. vs AUC of HOPE-2 score).

7. Discussion

We report one of the first studies, to the best of our knowledge, providing a simple clinical score for the prediction of long-term MACE and all cause death following COVID-19 hospitalization based on 5 clinical variables from a large multicenter international registry (HOPE-2 registry). In the present study, age, hypertension, history of cardiovascular disease, increased troponin serum levels at admission and acute renal failure during hospitalization were independent predictors of long-term MACE and all cause death and could be combined into a novel prognostic risk score. Furthermore, the newly developed HOPE-2 prognostic score accurately stratified the risk of long-term MACE and all cause death among hospitalized COVID-19 patients, and its performance was validated in an external cohort with good predictive value.

COVID-19 is a systemic disease with multi-organ involvement and a broad spectrum of manifestations[22,23]. As the population of patients recovering from COVID-19 grows, it is crucial to evaluate potential long-term consequences following this infection. Several patients described long-term symptoms following infection. Indeed, the presence of a clinical sequela at least 4 weeks after acute COVID-19 infection has been defined as PASC (Post-Acute Sequela of COVID-19) syndrome [24].

The incidence of PASC is 7.3 % in a large registry of 181,384 patients from United States of America, users of Veterans Health Administration [25]. The incidence rises up until 36 % among those patients hospitalized in ICU setting. Several multi-organ sequelae have been found involving respiratory (shortness of breath), cardiovascular (chest pain, and arrhythmia) and neurological system (headache and smell problems) with higher prevalence in females. Multi-organ sequelae were more pronounced in patients with high burden of comorbidities.

In a large prospective study from United Kingdom, factors associated with no full recovery at 1 year were female sex, obesity and invasive mechanical ventilation. Additionally increased levels of inflammatory mediators of tissue damage and repair, including Interleukin-6 concentration, were found among patients with incomplete recovery [26].

Similar data were reported from a large Chinese registry, Huang C et al. showed that the most common symptoms following COVID-19 are fatigue, sleep disorder, muscle weakness and anxiety or depression. Authors also found that patients with severe pulmonary insufficiency during hospitalization may present at follow-up impaired pulmonary diffusion capacities and abnormal chest imaging [27]. Another common sequela is postural orthostatic tachycardia that could reflect an autonomic dysfunction, which can be proven with head-up tilt table (HUTT) [28].

When evaluating long-term cardiovascular outcome following COVID-19, Xie Y et al. [7] found an increased risk of several cardiovascular disease, including cerebrovascular disorders (2.5 %), cardiac arrythmias (8 %), ischemic heart disease (4.5 %), heart failure (6 %) and

thrombotic disorders (5 %). Additional non-cardiovascular sequelae including diabetes, chronic respiratory failure, encephalopathy, peripheral neuropathy and amnesia (memory difficulty) have been reported from a large USA database [29].

Six months after infection, Al-Zahly et al. showed that, beyond the first 30 days of illness, compared to contemporary controls, patients showed a higher risk of death and incident post-acute sequelae including cardiovascular, coagulation and hematologic, metabolic, musculoskeletal, kidney, gastrointestinal, mental health and neurologic disorders [30].

Nunez et al. in an previous sub-analysis of this registry, including 9299 patients with a shorter follow-up (4 months) when compared to the present study (12 months), found that underlying heart disease and advance age were predictors of long-term prognosis [31].

According to the present study 7.8 % of patients following COVID-19 hospitalization experienced MACE or died at one year follow-up. A combination of baseline clinical features and in-hospital finding can stratify long-term risk.

Baseline clinical features as age, history of hypertension and history of cardiovascular disease are the risk factors included in the HOPE-2 score. Particularly age $>$ 75 years and history of cardiovascular disease have an important prognostic role in the score. Each one has 3 points and combined could represent a high-risk population. Moreover, hypertension is also a risk factor and could be associated to underlying endothelial dysfunctions and coagulopathy [32].

Additionally, hospitalization findings as increased troponin serum levels at admission and acute renal failure could better stratify long-term patient's risk. Increased admission troponin levels have been already evaluated in the context of COVID-19 hospitalization. Elevated troponin levels were associated with a 71 % increase in the risk of in-hospital death and with 2-fold increase in-hospital complications, including acute renal failure, sepsis, multiorgan failure, pulmonary embolism, and major bleeding [17]. Arcari et al. found that during COVID-19 hospitalization, isolated increase in troponin was associated with higher mortality rates despite low prevalence of cardio-vascular disease. Therefore, troponin levels could reflect a higher COVID-19-related systemic involvement [33].

Acute renal failure during COVID-19 hospitalization has an incidence that ranges from 6 % to 28 % [34] and is associated with systemic inflammatory and immune responses, endothelial injury and activation of coagulation pathways [35]. Jewell et al. found that, one third of patients (30.7 %) that experienced acute renal failure, had newly established renal impairment at three to six months [36]. As previously shown, acute renal failure has potential prognostic value during the first three years following the hospitalization and it could represent a valuable tool for scores evaluating the risk of MACE at one year following COVID hospitalization [37].

The present study evaluates a patient cohort who was not vaccinated for COVID-19 and shows an high rate of MACE at 1-year follow-up. Johnson et al. demonstrated that COVID-19 vaccination was associated with a significant reduction in all-cause hospitalizations and mortality rates in patients with heart failure [38]. Similar benefit has been proved also for receipt of influenza vaccination that was associated with a 34 % lower risk of MACE [39].

Recently, the 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in adults, proposed that clinical management of patients with previous COVID-19 hospitalization should be based on current guidelines and largely depend on the underlying symptoms [40]. Patients with history of cardiovascular disease, with documented cardiac complications during COVID-19 hospitalization or with persistent cardiopulmonary symptoms should undergo to a cardiological evaluation. The present proposed score could be helpful in stratify those patients that require strict cardiological follow-up. Considering the high burden of cardiovascular disease among general population and the COVID-19 pandemic, a dedicated cardiological ambulatory is needed for high risk COVID19 hospitalized patients.

8. Limitations

The HOPE-2 score was derived from a multicenter registry in which data were collected from several different institutions. The accuracy of the score is appreciable and comparable with other clinical scores but does not exceed 80 %, and some high-risk patients may have been missed.

Another limitation is that a certain number of patients were excluded from the analyses because of missing data regarding long-term MACE.

Patients recruitment was performed in both registries mainly from cardiology units and the prevalence of respiratory failure could be relative lower than reported in previous analyses.

9. Conclusions

The HOPE-2 prognostic score, a simple score based on 5 clinical and laboratory variables, may be useful for long-term risk stratification of COVID-19 hospitalized patients. High risk patients may deserve a strict follow-up.

Declaration of competing interest

None to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.03.002.

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