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Major adverse cardiovascular events (MACE) in patients with severe COVID-19 registered in the ISARIC WHO clinical characterization protocol: A prospective, multinational, observational study

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ABSTRACT

Purpose: To determine its cumulative incidence, identify the risk factors associated with Major Adverse Cardiovascular Events (MACE) development, and its impact clinical outcomes.
Materials and methods: This multinational, multicentre, prospective cohort study from the ISARIC database. We used bivariate and multivariate logistic regressions to explore the risk factors related to MACE development and determine its impact on 28-day and 90-day mortality.
Results: 49,479 patients were included. Most were male 63.5% (31,441/49,479) and from high-income countries (84.4% [42,774/49,479]); however, >6000 patients were registered in low-and-middle-income countries. MACE cumulative incidence during their hospital stay was 17.8% (8829/49,479). The main risk factors independently associated with the development of MACE were older age, chronic kidney disease or cardiovascular disease, smoking history, and requirement of vasopressors or invasive mechanical ventilation at admission. The overall 28-day and 90-day mortality were higher among patients who developed MACE than those who did not (63.1% [5573/8829] vs. 35.6% [14,487/40,650] $p < 0.001$; 69.9% [6169/8829] vs. 37.8% [15,372/40,650] $p < 0.001$, respectively). After adjusting for confounders, MACE remained independently associated with higher 28-day and 90-day mortality (Odds Ratio [95% CI], 1.36 [1.33–1.39];1.47 [1.43–1.50], respectively).
Conclusions: Patients with severe COVID-19 frequently develop MACE, which is independently associated with worse clinical outcomes.

Abbreviations list: ACE2, Angiotensin-Converting Enzyme 2; BNP, Brain Natriuretic Peptide; COVID-19, Corovarirus Disease 2019; EKG, Electrocardiogram; GSDMD, Gasdermin D; ICU, Intensive Care Unit; IL, Interleukin; IP, Interferon-g-induced protein; IQR, Interquartile Range; IRB, Institutional Review Board; MACE, Mayor Adverse Cardiovascular Events; MLKL, Mixed Lineage Kinase Domain-Like; pMLKL, phosphorylated Mixed Lineage Kinase Domain-Like; RIPK, Threonine-Protein Kinases; ROS, reactive Oxygen Species; RT-PCR, Reverse Transcription Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2.

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1. Introduction

COVID-19 has been one of the most catastrophic infectious diseases during the last 100 years, accounting for more than half a billion confirmed cases and almost 6 million deaths worldwide (https://covid19.who.int [1]). Hypoxia with secondary respiratory failure is manifested in up to 30% of the patients admitted to the hospital [2,3], resulting in worse clinical outcomes and higher associated medical costs [4]. SARS-CoV-2 invades the human cells using the angiotensin-converting enzyme (ACE) receptor [5], which is abundant in the upper and lower respiratory tract [6] and other tissues, inducing multiorgan failure or systemic complications [7]. It has been reported that up to 34% of patients with COVID-19 die due to systemic complications, including cardiovascular [8]. Indeed, studies have reported that the cardiovascular system could be affected in up to 25% of patients admitted to the hospital [8-11], causing Major Adverse Cardiovascular Events (MACE) such as acute myocardial injury (including infarctions), arrhythmia, heart failure, cardiac arrest, or stroke [12].

Patients with comorbidities often develop severe COVID-19, and MACE has been more frequently reported in those with severe COVID-19 and chronic medical diseases such as chronic cardiovascular disease, diabetes mellitus, hyperlipidaemia, and smoking [13-16]. Moreover, at the beginning of the pandemic, the need to improve clinical outcomes in this group of patients led to the indiscriminate use of several treatments. However, the international guidelines later discouraged using macrolides, hydroxychloroquine, convalescent plasma, and antiplatelets because their usage was proven ineffective and even toxic [17-19]. Notably, some of those medications have known cardiotoxic effects and have been linked to developing MACE in COVID-19 and other patients [20].

Severe COVID-19 patients are at higher risk of developing MACE during hospitalisation. It has been proposed that MACE is developed in response to severe systemic inflammation, up-regulation of the sympathetic neural system, direct cytotoxicity of circulating cytokines, destabilisation of coronary plaques, and direct viral injury to the cardiomyocytes [9]; However, the underlying mechanisms and risk factors associated with MACE development in patients with COVID-19 are not fully understood nor characterised, and their overall effect on clinical outcomes remains unknown [11,16,21,22]. Therefore, it is crucial to study MACE among patients with severe COVID-19 to determine the cumulative incidence of these complications, understand the risk factors (including comorbidities and treatments), and establish the clinical implications of MACE in these high-risk patients. The primary aim of this study is to determine the cumulative incidence of MACE in patients admitted to the hospital due to severe COVID-19 and the risk factors associated with its development. The secondary aim is to assess the impact of MACE on clinical outcomes (i.e., length of hospital stays [LOS] and 28-day and 90-day mortality rates).

2. Methods

This study is a secondary analysis of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset. The ISARIC and the World Health Organization (WHO) developed the Clinical Characterization Protocol for Severe Emerging Infections to provide a collaborative research framework for prospective observational data collection protocol on hospitalized patients with COVID-19 [23]. Information about the ISARIC-WHO clinical characterization protocol, case report forms, and consent forms are available in the online supplement of this manuscript and on the ISARIC website (https://isaric.org). For this analysis, investigators from 46 countries collected prospective data using the ISARIC Case Report Form (CRF) built on Research Electronic Data Capture (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tenn.) hosted by the University of Oxford. Investigators also collected data on locally hosted data systems and submitted data for centralised mapping to the ISARIC dataset. The data collection methods and characteristics have been described elsewhere [24].

The ISARIC-WHO Clinical Characterization Protocol was approved by the WHO Ethics Review Committee (RPC571 and RPC572). Local ethics approval was obtained for each participating country and site according to local requirements.

2.1. Study population

This analysis includes patients with laboratory-confirmed SARS-CoV-2 infection detected by reverse transcription-polymerase chain reaction (rtPCR) in a respiratory sample who were admitted to the hospital due to severe COVID-19 between January 17th and December 31st, 2021. We classify patients as severe COVID-19 if they require advanced respiratory support (i.e., Invasive Mechanical Ventilation [IMV], Non-Invasive Mechanical Ventilation [NIV], High Flow Nasal Cannula [HNC]) or treatment with vasopressors during the first 24 h of hospital admission. We excluded patients with >30% missing variables or without systemic complications reports and those without a reported outcome (i.e., survival or death), as we could not assess 28-day and 90-day mortality in those patients. Categorical variables have no missing data, and available information regarding numerical variables is shown on the corresponding Table.

2.2. Variables and measurements

Variables used in this analysis were age, sex, past medical history (i.e., comorbidities), national income classification according to the World Bank (https://data.worldbank.org/country), date of hospital admission, vital signs on hospital admission, laboratory results on admission, treatments used within the first 48 h of hospital admission (i.e., medications or interventions such as IMV), and systemic complications during hospitalisation. The grouping of diagnoses assigned to the systemic complications developed during the hospital stay can be found in the online supplement Table S1. All study variables were predefined in the ISARIC study protocol and case report form completion guide available online (https://isaric.org).

This cohort was stratified based on the development of MACE during the whole hospital admission. Patients who developed any cardiac complications were included in the MACE group, and patients without those complications were included in the non-MACE group.

2.3. Study definitions

MACE is a composite outcome, previously described in [12,25], including any of the following clinical diagnoses: *Cardiac arrhythmia* (new or worsening): change from the sequence of electrical impulses in the electrocardiogram (EKG), compared to EKG at hospital admission or in the past medical history [26]; *Heart Failure* (new or worsening): a clinical syndrome with symptoms and/or signs secondary to functional or structural cardiac abnormality, which may occur with or without previous cardiac disease documented through an echocardiogram, evidence of pulmonary or systemic congestion, and/or an increase of serum biomarker such the proB-type Natriuretic Peptide (Pro-BNP) [27]; *Myocardial injury*: acute cardiac cell injury corroborated by the rise of serum troponin values with at least one value above the 99th percentile of the normal reference value of each local laboratory; development of pathological Q waves and/or new ischemic changes in EKG; evidence of coronary thrombus by angiography and/or new loss of viable myocardium, or regional wall motion abnormality identified in the echocardiogram [28,29]; *Stroke* defined as a neurological deficit caused by an acute focal injury of the central nervous system by a vascular cause (i.e., cerebral infarction, intracerebral haemorrhage, or subarachnoid haemorrhage) [30]. The specific diagnosis in each MACE definition category is in the online supplement Table S2.

2.4. Statistical methods

The outcomes evaluated in this analysis were the risk factors for developing MACE anytime during hospital admission and the impact of MACE on 28-day and 90-day mortality rates. Categorical variables were expressed as counts (percentages). Non-normally distributed continuous variables were presented as median (interquartile range [IQR]), and normally distributed were expressed in mean (standard deviation [SD]). To determine the probability of MACE development in our study cohort during the follow-up time, the cumulative incidence was calculated using the reported number of new cases (i.e., patients who developed MACE during the hospital stay) over the total number of patients at risk (i.e., patients with and without any MACE diagnosis during the hospitalisation) who completed the observation period with a final disposition (i.e., discharge or death). Patients lost to follow-up or those who continued in the hospital when data were extracted for this analysis were not included in the denominator to calculate the cumulative incidence. Since the diseases included in MACE are not mutually exclusive, we present a Venn diagram that shows the frequency and interactions of such conditions in the population and their breakdown by age and gender (i.e., male and female) using stacked histograms. We also present an alluvia plot of the relationship between the patient's comorbidities and the development of the different diagnoses included in the MACE classification.

To determine the risk factors associated with the development of MACE and assess the clinical impact of MACE (i.e., 28-day and 90-day mortality), we performed bivariate and multivariate logistic regressions. Associations were initially explored through the Mann-Whitney *U* test for continuous variables and the Chi-squared test for categorical variables. The multivariate logistic regression models included risk factors with a *p*-value ≤ 0.2 as independent variables. Fit characteristics and results of the multivariate analysis can be found in the online supplement Fig. S1.

A minimum of 10 outcomes per variable included in the multivariate logistic regression analysis ensured the stability of the models, which were adjusted to select the best explicative model. To calculate the performance of each developed model, we computed the area under the model's receiver operating curve (AUROC). A 10-fold cross-validation method was used to evaluate the results of the statistical analyses that will generalise to an independent data set. The data set was divided into ten subsets, and the validation was repeated ten times. Each time, one of the subsets was used as the test cohort, and the other nine subsets were put together to form the training cohort. The average AUROC was then calculated across all ten trials.

We set the significance level at <0.001 and the confidence level at 95% to determine statistical differences between the variables because, in large datasets, such as the ISARIC COVID-19, minor differences could be identified as significant even when they are not clinically relevant. Data processing and statistical analysis were performed using Python version 3.9 with the following data packages: Pandas version 1.2.4, SciPy version 1.6.2, Scikit learn version 0.24.1, and Statsmodels version 0.12.2. For visualization, the following packages we used: Seaborn version 0.11.1, Plotly version 5.0.0, Matplotlib version 3.3.4, Zepid version 0.9.0, and Venn Diagram version 1.7.3 in R software.

3. Results

A total of 49,479 severe COVID-19 patients were included in the study (Fig. 1). Patients were enrolled in 54 countries. Most patients in the cohort were male (63.5% [31,441/49,479]) and from high-income countries (84.4% [42,774/49,479]); however, >6000 patients were registered in low-and-middle-income countries. The patients were

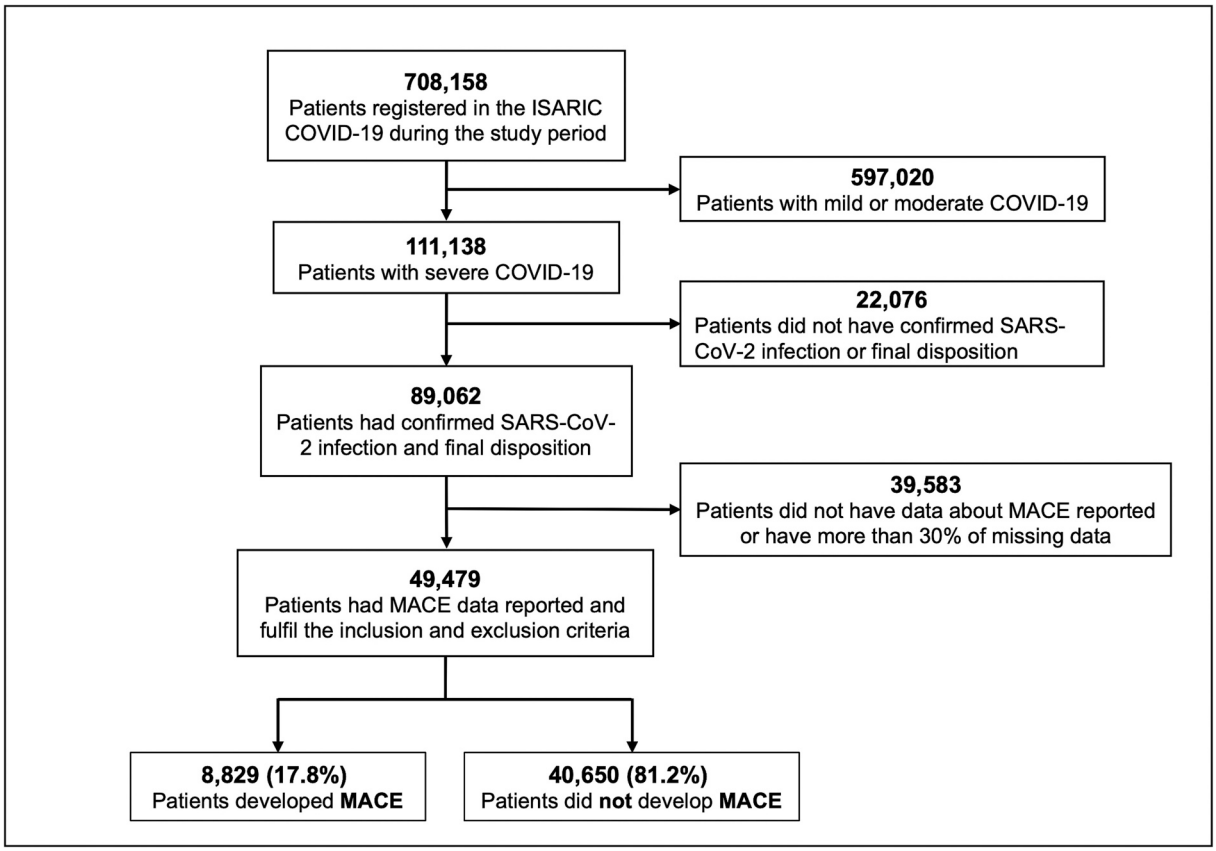

Fig. 1. Study flow chart. This figure presents the inclusion and exclusion criteria; the patients included in the study were stratified by patients that develop Major Adverse Cardiac Events (MACE).

mainly from the United Kingdom, followed by those from Pakistan, India, the United States of America, and Brazil. All demographic characteristics can be found in Table 1. The overall cumulative incidence of MACE during hospital admission was 17.8% (8829/49,479). The most frequent MACE diagnoses reported in the cohort were cardiac arrhythmia (36.9% [3254/8829]), followed by cardiac arrest (23.4% [2068/8829]) (Fig. 2a). Notably, several patients developed more than one cardiac complication.

3.1. Clinical features, treatments, and outcomes in MACE patients

Patients who developed MACE were older (69 years [58.0–78.0] vs 64 years [53.0–76.0]; $p < 0.001$), more often males between 60 and 79 years of age (Table 2, Fig. 2b). Compared to non-MACE patients, those with MACE presented more frequently with comorbidities, mainly those that are well-known risk factors for cardiovascular diseases, such as arterial hypertension (48.9% [4321/8829] vs. 40.1% [16,283/40,650]; $p < 0.001$), diabetes mellitus (37.1% [3274/8829] vs. 30.2% [12,269/40,650]; $p < 0.001$), and history of smoking (26.2% [2312/8829] vs. 22.8% [9273/40,650]; $p < 0.001$) (Fig. 3, Table 1).

Also, patients who developed MACE had higher median [IQR] heart rate (95.0 [81.0–110.0] vs 93.0 [81.0–106.0]; $p < 0.001$) and lower diastolic blood pressure (73.0 [63.0–83.0] vs 74.0 [66.0–83.0]; $p < 0.001$). Regarding laboratory results, they had higher leukocyte count (8.38 [5.8–12.5] vs. 7.8 [5.6–11.1]; $p < 0.001$), C-reactive protein (112.0 (53.0–192.0] vs 104 [52.0–175.0]; $p < 0.001$), and levels of kidney function tests (creatinine: 99.0 [74.3–145.0] vs 86.0 [68.0–115.8]; $p < 0.001$); blood urea nitrogen: 9.1 [6.0–15.0] vs 7.2 [4.9–11.9]; $p < 0.001$) (Table 2). Furthermore, MACE patients were more frequently admitted to the Intensive Care Unit (ICU) (67.0% [5916/8829] vs 49.3% [20,037/40,650]; $p < 0.001$), received more often IMV (53.0% [4680/8829] vs 28.9% [11,766/40,650]; $p < 0.001$) or NIV (51.3% [4529/8829] vs 49.4% [20,071/40,650]; $p = 0.001$), and vasopressor support (46.7% [4119/8829] vs 17.5% [7115/40,650]; $p < 0.001$) (Table 1).

Patients who developed MACE also had more systemic complications during hospital admission such as infections (i.e., co-infections, super-infections, or other infectious complications) (82.3% [7263/8829] vs 68.6% [27,895/40,650], $p < 0.001$); pulmonary complications (49.9% [4404/8829] vs 24.3% [9883/40,650] $p < 0.001$); renal complications (43.4% [3831/8829] vs 15.5% [6314/40,650] $p < 0.001$), among others (Table 1). When analysing the relationship between medical history and MACE, patients with diabetes mellitus and chronic kidney disease had a higher proportion of acute decompensation of their underlying comorbidity, as evident by a high correlation kappa coefficient (Fig. 4a). Patterns of treatments provided during acute illness were associated with comorbidities; as expected, the administration of salbutamol was preferred in patients with chronic pulmonary comorbidities (Fig. 4b). Treatments were also related to several comorbidities; a higher kappa coefficient was found among chloroquine/hydroxychloroquine with shock, clarithromycin with infectious complications, and tocilizumab with metabolic and hepatic complications (Fig. 4c).

Finally, patients who developed MACE had a longer LOS (median [IQR]:13.0 [7.0–23.0] vs 10.0 [6.0–18.0]; $p < 0.001$) (Table 1). In the Violin Plots presented in the online supplement Fig. S2, it is evident that most patients who did not develop MACE had a median LOS of around 10 days with few outliers, while those that presented MACE during hospital admission had a LOS skewed with a clear tendency towards more prolonged hospital stays. This tendency is also evident in older patients who developed MACE and had increased LOS compared to those who did not present MACE.

3.2. Risk factors for MACE

In the multivariate analysis, vasopressor requirement during the first 24 h of admission (OR [95%CI]: 1.44 [1.40, 1.47], $p < 0.001$), older age

Table 1
Characteristics, interventions, and outcomes comparing groups of patients that developed Major Adverse Cardiovascular Events (MACE) with patients that did not develop MACE in the selected cohort.

Variable	MACE	Non-MACE	*p*-value
	$n = 8829$	$n = 40,650$	
	(17.8%)	(81.2%)	
Demographics, n (%)			
High-income country	7664 (86.8)	35,110 (86.4)	0.29
Female	2847 (32.2)	15,191 (37.4)	<0.001
Comorbidities, n (%)			
Anemia	47 (0.5)	203 (0.5)	0.75
Asthma	1105 (12.5)	5307 (13.1)	0.18
Benign neoplasm	1 (0.0)	5 (0.0)	0.65
Cardiomyopathy	2 (0.0)	9 (0.0)	0.72
Cardiovascular arrhythmia	84 (1.0)	158 (0.4)	<0.001
Chronic kidney disease	1446 (16.4)	4214 (10.4)	<0.001
Chronic pulmonary disease (not asthma)	1411 (16.0)	5347 (13.2)	<0.001
Congestive heart failure	7 (0.1)	4 (0.0)	<0.001
Dementia	509 (5.8)	2441 (6.0)	0.40
Diabetes mellitus	3274 (37.1)	12,269 (30.2)	<0.001
HIV	36 (0.4)	158 (0.4)	0.87
Hematic malignancies	20 (0.2)	69 (0.2)	0.32
Hypertension	4321 (48.9)	16,283 (40.1)	<0.001
Hypothyroidism	247 (2.8)	1059 (2.6)	0.32
Immunosuppression	216 (2.4)	746 (1.8)	<0.001
Ischemic heart disease	13 (0.1)	19 (0.0)	<0.01
Lipid disorder	137 (1.6)	362 (0.9)	<0.001
Liver disease	295 (3.3)	1104 (2.7)	0.001
Malignant neoplasm	854 (9.7)	3020 (7.4)	<0.001
Neoplasm (unspecified)	9 (0.1)	25 (0.1)	0.28
Rheumatological disorder	792 (9.0)	3324 (8.2)	0.01
Smoking	2312 (26.2)	9273 (22.8)	<0.001
Solid tumor	80 (0.9)	300 (0.7)	0.12
Stroke	53 (0.6)	177 (0.4)	0.05
Complications, n (%)			
Autoimmunity	3 (0.0)	10 (0.0)	0.90
Coagulopathies	1234 (14.0)	1612 (4.0)	<0.001
Gastrointestinal	370 (4.2)	623 (1.5)	<0.001
Hematological	2753 (31.2)	4735 (11.6)	<0.001
Hemodynamic	588 (6.7)	646 (1.6)	<0.001
Infectious	7263 (82.3)	27,895 (68.6)	<0.001
Renal	3831 (43.4)	6314 (15.5)	<0.001
Hepatic	1620 (18.3)	2740 (6.7)	<0.001
Metabolic	2557 (29.0)	5027 (12.4)	<0.001
Musculoskeletal	163 (1.8)	213 (0.5)	<0.001
Neurological	621 (7.0)	1113 (2.7)	<0.001
Other	2639 (29.9)	7459 (18.3)	<0.001
Pulmonary	4404 (49.9)	9883 (24.3)	<0.001
Treatments, n (%)			
High flow nasal canula	4914 (55.7)	25,746 (63.3)	<0.001
Non-invasive mechanical ventilation	4529 (51.3)	20,071 (49.4)	0.001
Invasive mechanical ventilation	4680 (53.0)	11,766 (28.9)	<0.001
Vasopressor	4119 (46.7)	7115 (17.5)	<0.001
Intensive Care Unit	5916 (67.0)	20,037 (49.3)	<0.001
Clarithromycin	2625 (29.7)	12,404 (30.5)	0.15
Remdesivir	1628 (18.4)	8657 (21.3)	<0.001
Amoxicillin	1409 (16.09)	7539 (18.5)	<0.001
Salbutamol	1163 (13.2)	5665 (13.9)	0.06
Azithromycin	1105 (12.5)	3892 (9.6)	<0.001
Tocilizumab	698 (7.9)	3392 (8.3)	0.18
Colchicine	53 (0.6)	205 (0.5)	0.29
Corticosteroids	5595 (63.5)	26,085 (61.7)	0.004
Chloroquine/hydroxychloroquine	340(3.9)	901 (2.2)	<0.001
Outcomes			
28-day mortality, n (%)	5573 (63.1)	14,487 (35.6)	<0.001
90-day mortality, n (%)	6169 (69.9)	15,372 (37.8)	<0.001
Hospital length of stay, median (IQR)	13.0 (7.0–23.0)	10.0 (6.0–18.0)	<0.001

Abbreviations: MACE (Major adverse cardiovascular event), Non-MACE (Non-Major adverse cardiovascular event), HIV (Human immunodeficiency virus), IQR (Interquartile range).

(OR [95%CI]: 1.22 [1.19, 1.24], $p < 0.001$), treatment with IMV during the first 24 h of hospital admission (OR [95%CI]: 1.17 [1.14, 1.20], $p < 0.001$), history of chronic kidney disease (OR [95%CI]: 1.09 [1.07, 1.11], $p < 0.001$), NIV or HFNC during the first 24 h of hospital admission (OR [95% CI]: 1.05 [1.03–1.07], $p < 0.001$; 1.05 [10.3–1.07, $p < 0.001$]; respectively), history of smoking (OR [95% CI]: 1.04 [1.02–1.06], $p < 0.001$), and previous diagnosis of cardiac arrhythmia (OR [95% CI]: 1.04 [1.02–1.06], $p < 0.001$) were the main risk factors for the development of MACE with a mean AUROC [SD] of 0.72 [±0.02] (Fig. 5, online supplement Table S3).

Medications with potential cardiotoxicity such as azithromycin (OR [95% CI]:1.03 [1.01–1.04], $p = 0.01$) and clarithromycin (OR [95% CI]:1.02 [1.00–1.04], $p = 0.02$) were associated with the development of MACE, though not meeting the stricter significance level set at $p < 0.001$. In contrast, chloroquine/hydroxychloroquine did not show a statistically significant relationship after the covariate adjusting (OR [95% CI]:1.02 [1.00–1.04], $p = 0.10$). All variables included in the multivariate analysis are presented in Fig. 5 and the online supplement Table S3.

A multivariate analysis was also performed to identify the risk factors related to each individual category of MACE. These results can be found in Supplement Table S4 for cardiac arrhythmia, Table S5 for heart failure, Table S6 for myocardial injury, Table S7 for stroke, and Table S8 for cardiac arrest.

3.3. Risk factors for 28-day and 90-day mortality

Mortality was significantly higher in patients who developed MACE at both 28-day and 90-day (63.1% [5573/8829] vs 35.6% [14,487/40,650]; $p < 0.001$) and (69.9% [6169/8829] vs 37.8% [15,372/40,650]; $p < 0.001$) respectively (Table 1). As evidenced in Fig. 6a and Supplement Table S9, older age (OR [95% CI]: 2.26 [2.20–2.32], $p < 0.001$), higher leukocytes counts (OR [95% CI]:1.50 [1.42–1.59], $p < 0.001$), and treatment with IMV (OR [95% CI]:1.37 [1.33–1.41], $p < 0.001$) were the main risk factors to predict 28-day mortality with a mean AUROC [SD] of 0.80 [±0.04] (Supplement Fig. S3). Notably, we found that MACE development during hospital admission was independently associated with 28-day mortality (OR [95% CI]:1.36 [1.33–1.39], $p < 0.001$) (Fig. 6a and Supplement Table S9).

Regarding 90-day mortality, older age (OR [95% CI]: 2.44 [2.37–2.51], $p < 0.001$), IMV requirement (OR [95% CI]:1.52 [1.47–1.56], $p < 0.001$), higher leukocytes level (OR [95% CI]:1.48 [1.40–1.56], $p < 0.001$), higher urea nitrogen levels (OR [95% CI]:1.37 [1.33–1.42], $p < 0.001$), vasopressor treatment (OR [95% CI]: 1.29 [1.25–1.33], $p < 0.001$), and NIV (OR [95% CI]: 1.27 [1.24–1.30], $p < 0.001$) were the main risk factors identified with a mean AUROC [SD] of 0.81 [±0.03] (Supplement Fig. S4). MACE was, again, independently associated with 90-day mortality (OR [95% CI]: 1.47 [1.43–1.50], $p < 0.001$) (Fig. 6b and Supplement Table S10).

A sensitivity analysis for patients presenting MACE without cardiac arrest was also performed and found that the results did not change. These results can be found in Supplement Table S11 and Fig. S5 for 28-day mortality, and Table S12 and Fig. S6 for 90-day mortality

4. Discussion

In this study, we found an incidence of MACE in one out of every five to six patients admitted to the hospital due to severe COVID-19, making it a complication of broad clinical interest in this group of patients. The most frequent clinical diagnoses of MACE were cardiac arrhythmias, cardiac arrest, and heart failure. Older age, history of smoking, renal or cardiovascular comorbid conditions, and the requirement of vasopressors or ventilator support at hospital admission were the main risk factors independently associated with its development. Other variables, such as macrolide treatment, were related to MACE development but did not accomplish the statistical significance threshold (i.e., p-value <0.001). MACE during hospital admission significantly increased the 28-day and 90-day mortality risk in patients with severe COVID-19 and impacted other outcomes, such as prolonged LOS.

MACE is widely described in the literature and associated with different lower respiratory tract infections. Instance, in pneumococcal and influenza infection, up to 30% of the patients develop MACE [12,31], and it is strongly related to acute myocardial infarction and cardiovascular death [32,33]. However, definitions vary, making it challenging to derive its actual cumulative incidence in patients with COVID-19. It has been estimated that up to 25% of patients might develop one MACE during their hospital stay [8,9]. Specifically, Shaobo Shi et al. found cardiac injury in 19.7% of patients [21]. Vicent Labbé et al. described an incidence of myocardial infarction as high as 57.6% in a cohort of 92 patients [16]. Juan R Rey et al. found a heart failure rate of 4.9% of patients in a cohort of 3080 patients [22]. These findings are heterogeneous, using different methodologies, and importantly, only represent a group of patients that develop MACE without considering the total population at risk. In contrast, our study used a multinational prospective cohort of patients with severe COVID-19 and found that

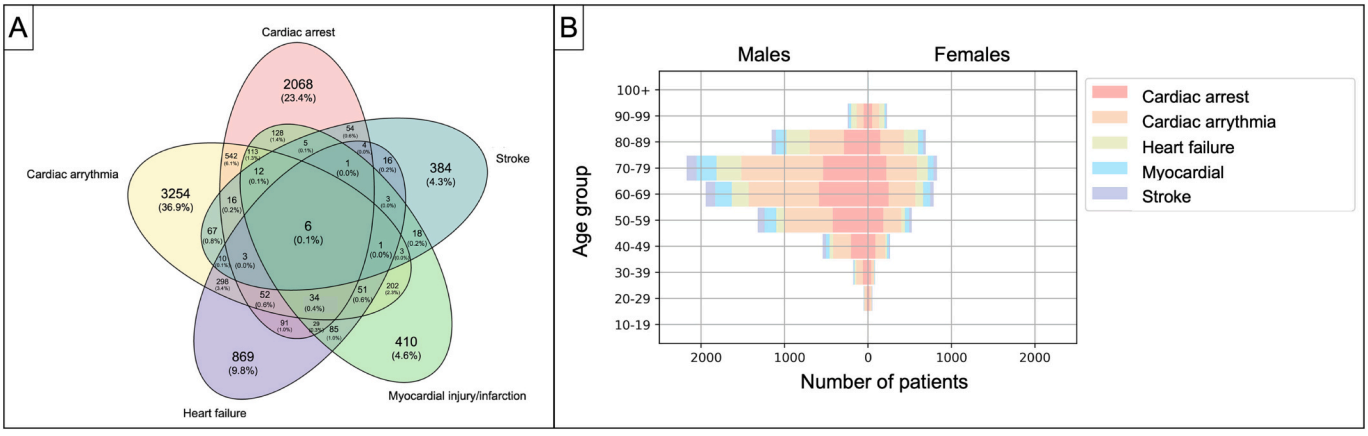

Fig. 2. Clinical diagnosis of Major Adverse Cardiovascular Events (MACE) and its prevalence by sex and age group. In *panel A,* we present a Venn diagram with the number of patients suffering from each clinical diagnosis included in MACE. The percentages are calculated based on the number of patients that developed MACE. In *panel B,* we present the number of patients broken down by age and sex. The bar is filled with the number of patients that developed each clinical diagnosis included in MACE per age group.

Table 2
Vital signs and laboratory tests comparing groups of patients that developed Major Adverse Cardiovascular Events (MACE) with patients that did not develop MACE in the selected cohort.

Variable	MACE		Non-MACE		*p*-value
	n	Median (IQR)	n	Median (IQR)	
Demographics					
Age	8829	69.0 (58.0–78.0)	40,650	64.0 (53.0–76.0)	<0.001
Vital signs					
Heart rate (beats/min)	8692	95.0 (81.0–110.0)	39,969	93.0 (81.0–106.0)	<0.001
Diastolic blood pressure (mmHg)	8679	73.0 (63.0–83.0)	40,098	74.0 (66.0–83.0)	<0.001
Systolic blood pressure (mmHg)	8687	129.0 (112.0–145.0)	40,136	129.0 (115.0–144.0)	0.05
Temperature (C°)	8548	37.2 (36.6–38.1)	39,978	37.3 (36.7–38.1)	<0.001
Laboratory test					
Urea nitrogen (mmol/L)	7820	9.1 (6.0–15.0)	35,540	7.2 (4.9–11.9)	<0.001
C-reactive protein (mg/L)	6204	112.0 (53.0–192.0)	27,922	104.0 (52.0–175.0)	<0.001
Respiratory rate (breaths/min)	8524	24.0 (20.0–30.0)	39,578	24.0 (20.0–29.0)	<0.001
Oxygen saturation (%)	8669	93.0 (88.0–96.0)	39,479	94.0 (89.0–96.0)	<0.001
Hemoglobin (g/L)	8440	131.0 (114.0–146.0)	38,673	133.0 (118.0–146.0)	<0.001
Platelets (10^9/L)	8447	203.0 (149.0–269.0)	38,758	203.0 (148.0–268.0)	0.028
Creatinine (umol/L)	7113	99.0 (74.3–145.0)	32,267	86.0 (68.0–115.8)	<0.001
Sodium (mmol/L)	6398	136.0 (133.0–140.0)	29,006	136.0 (133.0–139.0)	0.05
Leukocytes (10^9/L)	8518	8.38 (5.8–12.5)	39,087	7.8 (5.6–11.1)	<0.001

Abbreviations: MACE (Major adverse cardiovascular event), Non-MACE (Non-Major adverse cardiovascular event), IQR (Interquartile range).

17.8% of patients with severe COVID-19 developed one or more MACE-defining conditions at some point during their hospital stay. Differences between this and prior studies are mainly accounted for by the methodological limitations of the previous studies, where selection bias and preliminary calculation of the cumulative incidence might lead to an overestimation of the incidence of MACE in the general population.

Identifying risk factors associated with MACE development is fundamental to taking early measures to improve the patient's prognosis. The expert consensus of the American College of Cardiology on cardiovascular sequelae of COVID-19 concluded that age and pre-existing cardiovascular disease were directly related to myocardial injury in these patients [21,22,34,35]. On the contrary, Zhi-Chun Gu et al. conducted a meta-analysis to assess myocardial injury in 53 studies involving 7679 patients. They found no association – while recognising the number of studies included and the sample size as a limitation that affects the robustness of results [36]. Our results complement the evidence in this regard, showing that the requirement of vasopressors or ventilator support in the first days of hospital admission in critical COVID-19 patients increases the cardiovascular risk and the development of severe complications like MACE [21,37,38]. These findings are significant as they show that not all patients with severe COVID-19 are alike. Personalised assessment should be carried out to determine the risk factors for worse outcomes and identify the best treatments.

Macrolide treatment was widely recommended at the beginning of the pandemic to modulate the severe inflammatory reaction observed in these patients [39-41]. These medications are known to prolong the QT segment and facilitate MACE. Ioannis Farmakis et al. meta-analysis of 3088 COVID-19 patients found that azithromycin treatment was associated with QTc prolongation in 13% (95% CI: 9–18) of patients [42]. However, heterogenicity between the 34 selected studies was high, mainly for the differences in comorbidities and disease severity. Likewise, a systematic review published in the Cochrane Database did not find a statistically significant association of cardiovascular adverse effects with the use of azithromycin in COVID-19 patients (RR [95% CI]: 0.92; [0.73 a 1.15]) [43]. Our study found that macrolide treatment was related to an increased risk of MACE development; however, this association was not significant based on the statistical significance threshold in our study. Therefore, we could not confirm that treatment with macrolides was significantly associated with MACE. However, these results may contribute to the available literature on these patients.

The development of MACE during admission due to severe COVID-19 has been associated with increased mortality risk in small cohort studies. Tao Guo et al. found in a cohort of 187 patients admitted due to COVID-19 that hospital mortality increased by 69.4% in those patients with cardiovascular disease who developed myocardial injury [44]. In

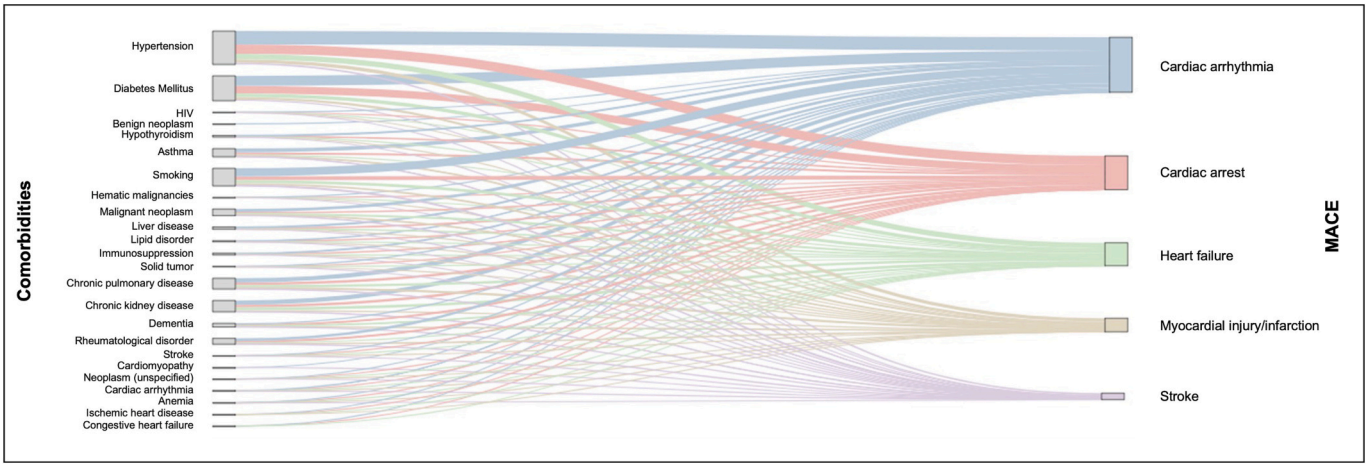

Fig. 3. An Alluvial plot of the relation between comorbidities and Major Adverse Cardiovascular Events (MACE). This figure illustrates the frequency of comorbid conditions stratified by each clinical diagnosis included in MACE.

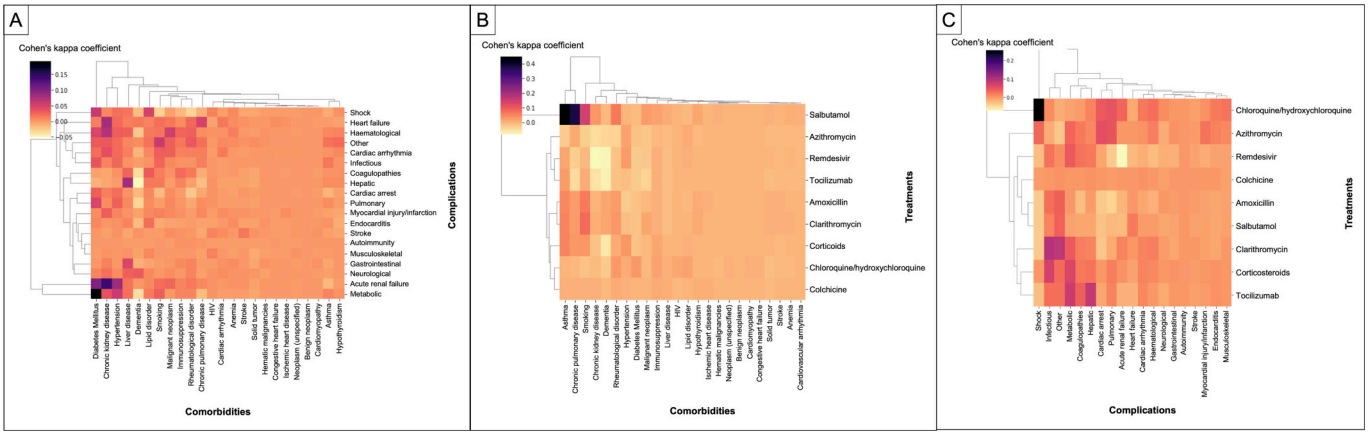

Fig. 4. Relations among comorbid conditions, systemic complications, and treatments utilised during the hospitalisation due to severe COVID-19. These heat maps with dendrograms illustrate the correlation between comorbid conditions, complications, and treatments. In *panel A* the colour scale of each cell shows the concordance between each of the evaluated comorbid conditions and the complications developed by the patients. In *panels B and C*, the colour scale of each cell, respectively, shows the concordance between the previous comorbid conditions or complications reported at hospital admission with the treatments received. Dendrograms show the hierarchical clustering of the nine treatments (y-axis) and the complications or comorbidities.

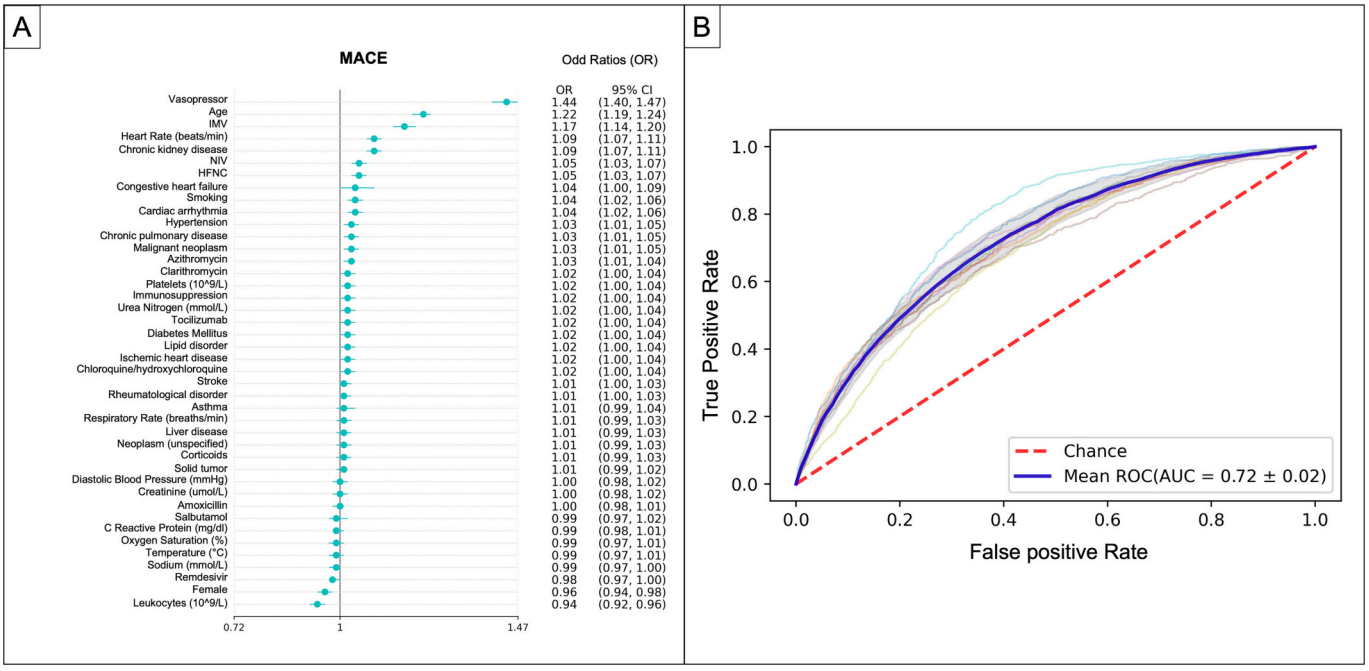

Fig. 5. Multivariate model to identify the risk factors associated with the development of Major Adverse Cardiovascular Events (MACE). *Panel A* shows the forest plot of the Odds Ratios (OR) obtained in the logistic regression of the different risk factors included in the model. Mean closed circles present ORs, and whiskers represent the 95% confidence interval (95% CI). *Panel B* shows the cross-validation ROC curves and area under the curve (AUC) of the model developed.

another retrospective cohort study of 418 patients with confirmed COVID-19, Shaobo Shi et al. found an in-hospital mortality rate of up to 51.2% and a mortality HR of 4.26 [95% CI:1.92–9.49] for patients who developed a cardiac complication during the hospital stay [21]. Annapoorna Kini et al. performed a multicentre retrospective study of 4695 COVID-19 patients and reported that 47.3% developed acute myocardial injury and died at six months of follow-up (HR 4.72, 95% CI: 4.15–5.36; $P < 0.001$) [45]. Our findings concur with these small cohorts, bringing the strength of a robust statistical analysis of a large number of patients in >40 countries. We provide clear evidence that the development of MACE in patients with severe COVID-19 increased the risk of death dramatically at 28 and 90 days by approximately 40%, which is a novel finding. Thus, physicians should remember that COVID-19 patients might develop MACE after the acute episode and should be monitored for early diagnosis and potentially secondary prevention.

Finally, some researchers have attempted to identify potential preventive strategies. For instance, Kim YE et al. utilised a retrospective cohort of 231,037 in Korea to study the effect of the anti-COVID-19 vaccine (i.e., mRNA vaccines) on the development of myocardial infarction and ischemic stroke, two diagnoses included in MACE [46]. The authors found that patients that were fully vaccinated against COVID-19 were not only protected from the development of severe infection but also had a lower risk of developing myocardial infarction (adjusted HR [95% CI]: 0.48 [0.25–0.94]) and ischemic stroke (adjusted HR [95% CI]: 0.40; [0.26–0.63]). These data highlight the importance of vaccination, especially in high-risk patients; it also shows that the risk of MACE can be reduced by interventions that prevent severe COVID-19. However, specific medications to prevent MACE in COVID-19 have

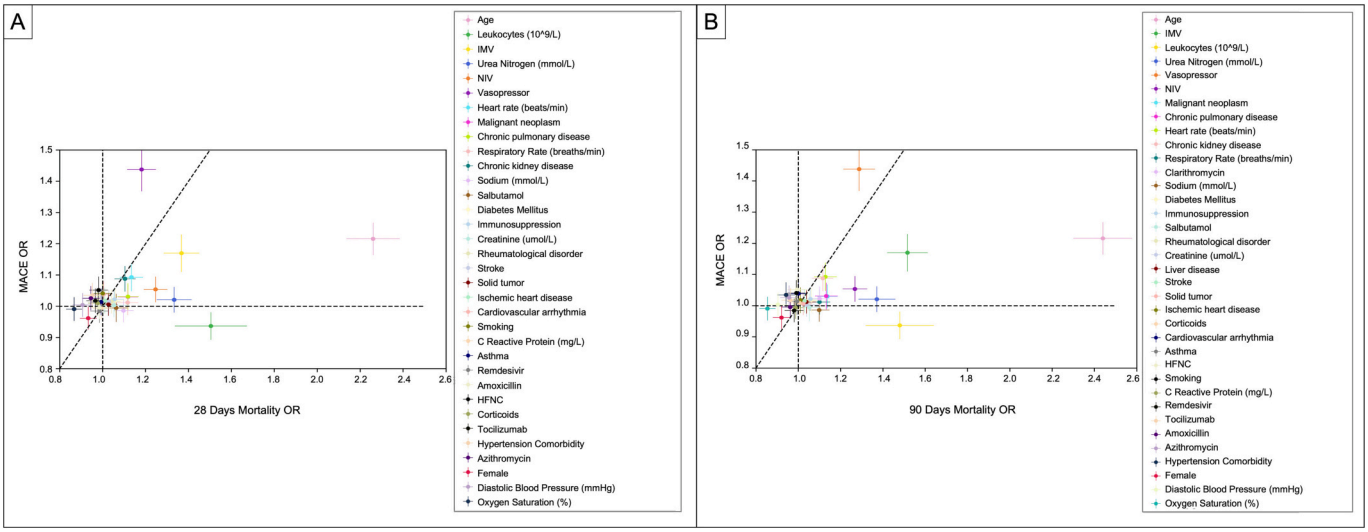

Fig. 6. Relation among the Odd Ratios (OR) obtained in the models to predict Major Adverse Cardiovascular Events (MACE) and 28-day or 90-day mortality. The circles represent the mean of each OR obtained in the model to identify the risk factors for MACE (y-axis) and the model to identify risk factors for 28-day mortality (x-axis, *panel A*) or 90-day mortality (x-axis, *panel B*). All error bars represent the 95% confidence interval (95% CI). Horizontal and vertical dotted lines separate the variables as protective or risky, and the diagonal dotted line is a visual reference to assess the association between the ORs.

not been described.

Several medications could be explored to prevent the development of MACE. For example, antiplatelets, ineffective in preventing severe disease or improving mortality in COVID-19 patients, could reduce the risk of developing MACE. Other "cardioprotective" medications, such as statins, ACE inhibitors, or beta-blockers, could also be explored to treat patients with COVID-19 to prevent the development of MACE. However, it is unclear whether these medications could effectively prevent MACE and should be explored in future research projects. Notably, secondary analyses of some of the large platform trials where some of these medications were tested (e.g., the RECOVERY trial or the REMAP-CAP study) could be used to answer these questions.

This study has some strengths and limitations that are important to discuss. First, it is critical to remember that one of the biggest strengths of this study is also a limitation, the large sample size. It is known that having large cohorts might lead to identifying minor differences that could not be clinically significant or practical. We increased the significance threshold to <0.001 to establish statistical differences to overcome this problem. Secondly, our study is a multicentre collaboration. However, clinical definitions were provided to all researchers in the ISARIC-WHO case record form; we do not know how these were applied in each institution to identify the clinical components that constitute a MACE diagnosis. Fortunately, the diagnosis of cardiovascular complications included in the MACE definition is globally standardised in openly available international guidelines, which reduces the risk of bias in our results. However, some residual underdiagnosis could exist as ECGs and echocardiograms were not collected. Thirdly, we did not adjust the models for a single severity score, comorbidities, vital signs on admission, laboratories on entry, and treatments received in the first 48 h of the hospital admission were included as independent variables for adjusting confounding variables. Finally, we do not know the treatments used by all local investigators for MACE or the vaccination status of the patients; therefore, the impact of these treatments on the clinical outcomes is not assessed in this study. However, strict statistical adjustments developed through Logistic Regression Analysis were used to determine the independent impact of MACE on mortality. Further studies are needed to compare our findings related to COVID-19 complications.

5. Conclusion

In conclusion, MACE frequently occurs in patients with severe COVID-19 and tremendously impacts clinical outcomes. Early identification of patients at higher risk of developing MACE is essential to establish preventive interventions and comprehensive monitoring strategies to diagnose and treat these complications early to improve clinical outcomes. International guidelines to treat the specific pathologies included in MACE should be applied to patients with severe COVID-19 that develop these complications during hospital admission. Further studies are needed to understand the underlying mechanisms of MACE and identify potential therapeutic targets.

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Availability of data and materials

The dataset is available through the Infectious disease Data Observatory website (https://www.iddo.org).

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Appendix A. Supplementary data

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