J Crit Care 77 (2023) 154318

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

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

Luis Felipe Reyes [a,b,c,*], Esteban Garcia-Gallo [a,c], Srinivas Murthy [d], Yuli V. Fuentes [a], Cristian C. Serrano [a,b], Elsa D. Ibáñez-Prada [a,b], James Lee [c], Amanda Rojek [c], Barbara Wanjiru Citarella [c], Bronner P. Gonçalves [c], Jake Dunning [c], Indrek Rätsep [c], Andre Emilio Viñan-Garces [a], Christiana Kartsonaki [c], Jordi Rello [e,f], Ignacio Martin-Loeches [g], Manu Shankar-Hari [h], Piero L. Olliaro [c], Laura Merson [c], The ISARIC Characterisation Group [1]

[a] Universidad de La Sabana, Chía, Colombia
[b] Clínica Universidad de La Sabana, Cundinamarca, Colombia
[c] Pandemic Sciences Institute, University of Oxford, Oxford, United Kingdom
[d] Department of Pediatrics, University of British Columbia, Vancouver, Canada
[e] Clinical Research/Epidemiology in Pneumonia & Sepsis (CRIPS), Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain
[f] Centro de Investigación Biomédica En Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[g] Department of Clinical Medicine, St James's Hospital, Multidisciplinary Intensive Care Research Organization (MICRO), Dublin, Ireland
[h] Centre for Inflammation Research, University of Edinburgh; 47 Little France Crescent, Edinburgh, Scotland, United Kingdom

ARTICLE INFO

Keywords:
Major adverse cardiovascular events (MACE)
COVID-19
Mortality
Complications

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.

* Corresponding author at: Universidad de La Sabana, Chía, Colombia.
E-mail address: luis.reyes5@unisabana.edu.co (L.F. Reyes).

[1] The Complete list of authors and affiliations is listed at the end of the manuscript.

https://doi.org/10.1016/j.jcrc.2023.154318

Available online 9 May 2023
0883-9441/© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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

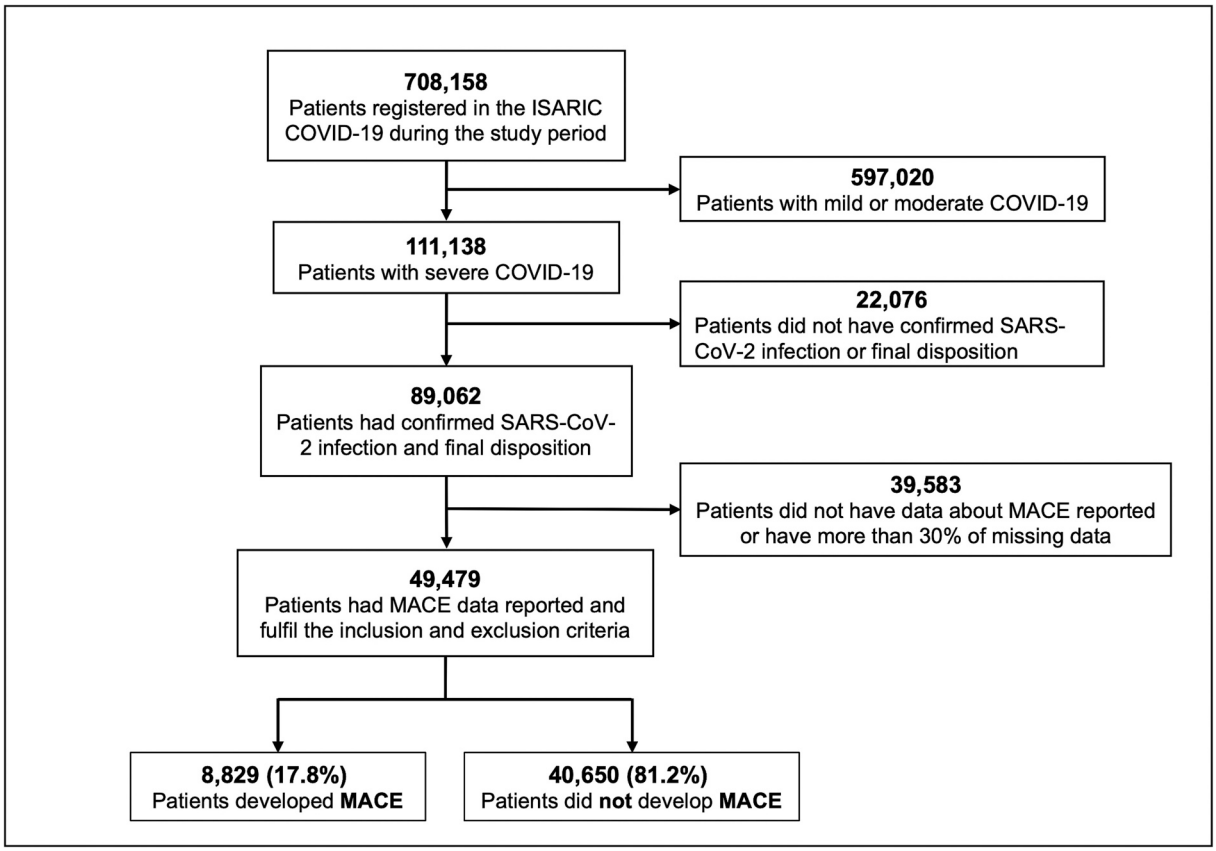


Fig. 1. Study flow chart. This figure presents the inclusion and exclusion criteria; the patients included in the study were stratified by patients that develop Major Adverse Cardiac Events (MACE).

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

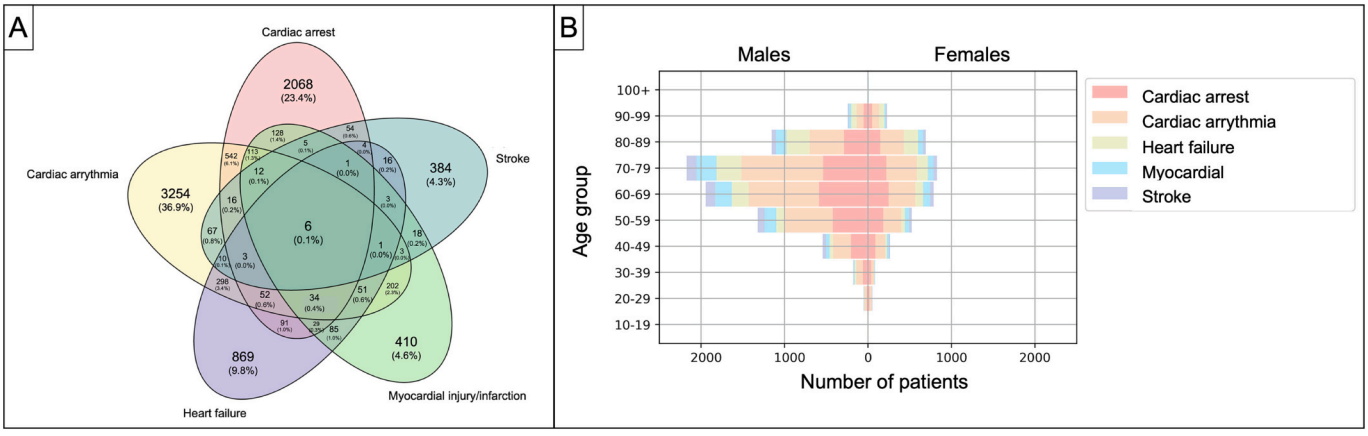


Fig. 2. Clinical diagnosis of Major Adverse Cardiovascular Events (MACE) and its prevalence by sex and age group. In *panel A,* we present a Venn diagram with the number of patients suffering from each clinical diagnosis included in MACE. The percentages are calculated based on the number of patients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

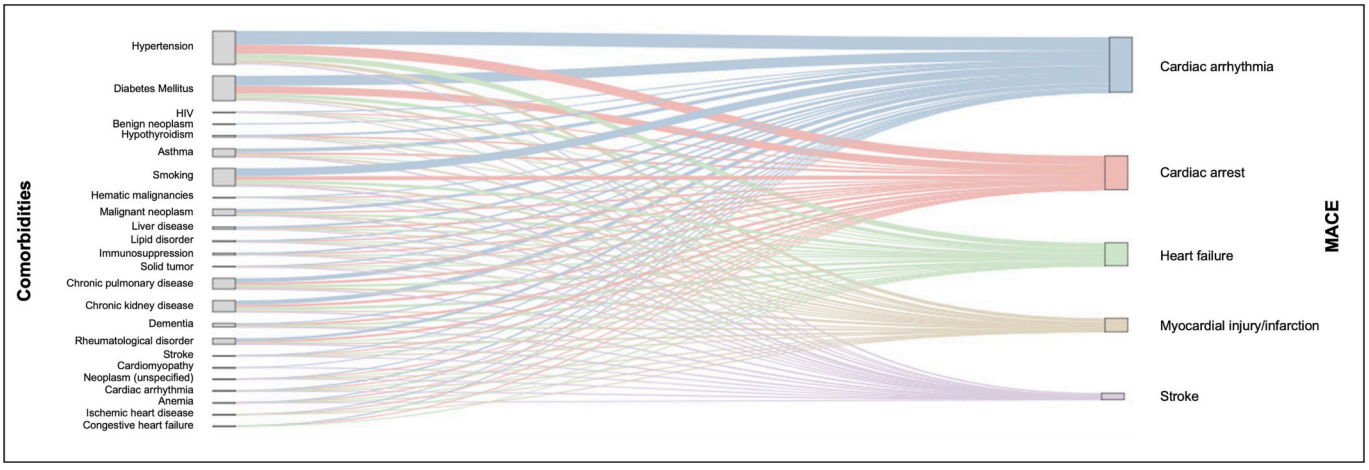


Fig. 3. An Alluvial plot of the relation between comorbidities and Major Adverse Cardiovascular Events (MACE). This figure illustrates the frequency of comorbid conditions stratified by each clinical diagnosis included in MACE.

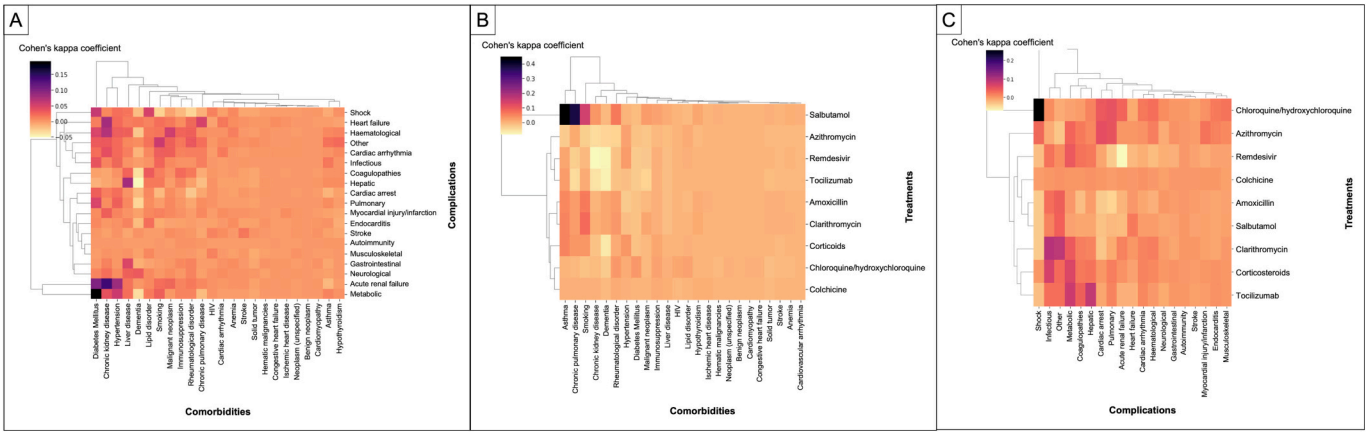


Fig. 4. Relations among comorbid conditions, systemic complications, and treatments utilised during the hospitalisation due to severe COVID-19. These heat maps with dendrograms illustrate the correlation between comorbid conditions, complications, and treatments. In *panel A* the colour scale of each 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.

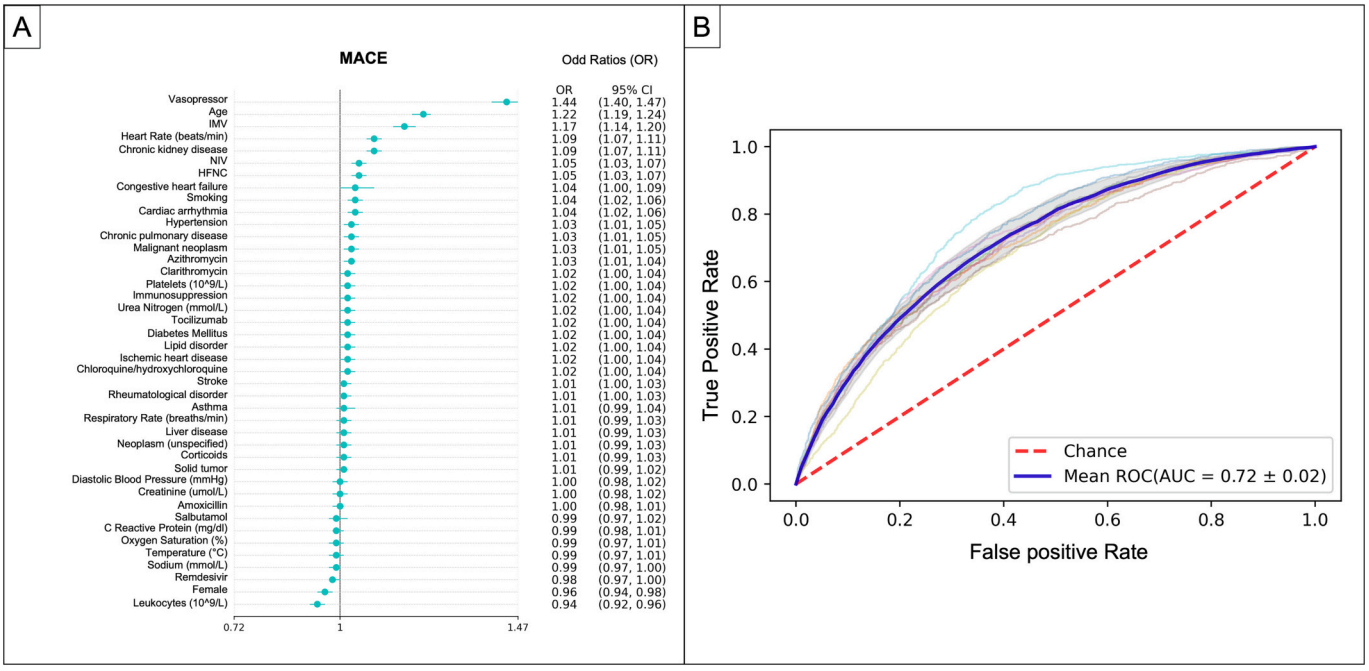


Fig. 5. Multivariate model to identify the risk factors associated with the development of Major Adverse Cardiovascular Events (MACE). *Panel A* shows the forest plot of the Odds Ratios (OR) obtained in the logistic regression of the different risk factors included in the model. Mean closed circles present 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

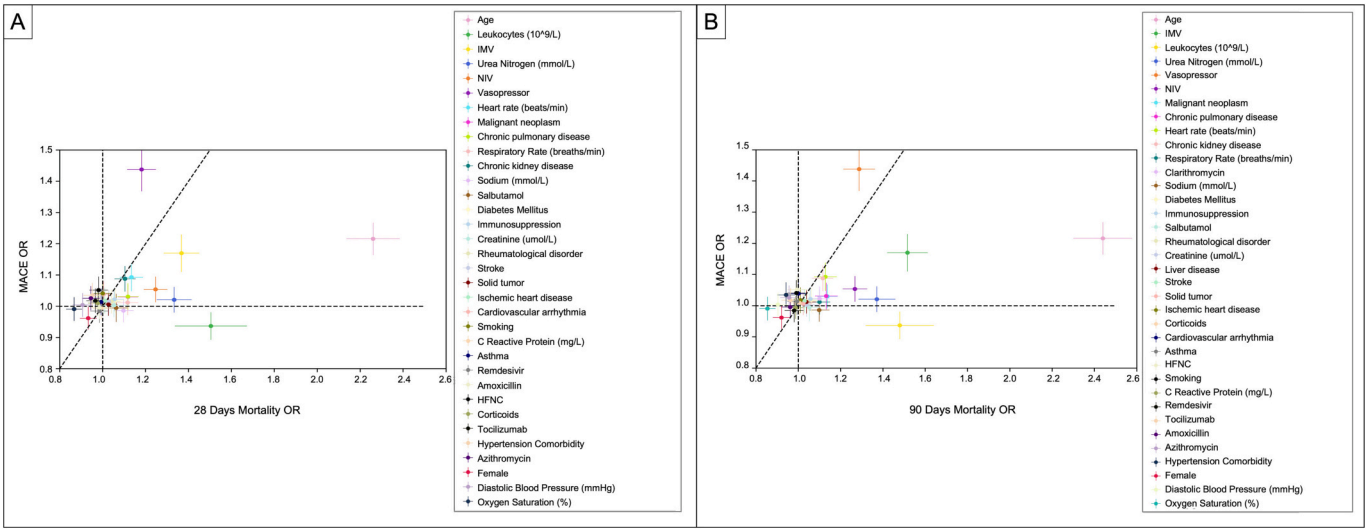


Fig. 6. Relation among the Odd Ratios (OR) obtained in the models to predict Major Adverse Cardiovascular Events (MACE) and 28-day or 90-day mortality. The circles represent the mean of each OR obtained in the model to identify the risk factors for MACE (y-axis) and the model to identify risk factors 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.

ISARIC Clinical Characterization Group Authors

Ali Abbas, Sheryl Ann Abdukahil, Nurul Najmee Abdulkadir, Ryuzo Abe, Franklina Korkor Abebrese, Laurent Abel, Amal Abrous, Lara Absil, Subhash Acharya, Andrew Acker, Francisca Adewhajah, Diana Adrião, Saleh Al Ageel, Shakeel Ahmed, Kate Ainscough, Tharwat Aisa, Takako Akimoto, Ernita Akmal, Razi Alalqam, Tala Al-dabbous, Senthilkumar Alegesan, Beatrice Alex, Kévin Alexandre, Abdulrahman Al-Fares, Huda Alfoudri, Imran Ali, Kazali Enagnon Alidjnou, Jeffrey Aliudin, Qabas Alkhafajee, Clotilde Allavena, Nathalie Allou, Aneela Altaf, João Alves, João Melo Alves, Rita Alves, Maria Amaral, Nur Amira, Phoebe Ampaw, Roberto Andini, Claire Andrejak, Claire Andréjak, Andrea Angheben, François Angoulvant, Sophia Ankrah, Séverine Ansart, Sivanesen Anthonidass, Massimo Antonelli, Ardiyan Apriyana, Yaseen Arabi, Irene Aragao, Francisco Arancibia, Carolline Araujo, Antonio Arcadipane, Patrick Archambault, Lukas Arenz, Jean-Benoît Arlet, Christel Arnold-Day, Lovkesh Arora, Rakesh Arora, Elise Artaud-Macari, Diptesh Aryal, Angel Asensio, Muhammad Ashraf, Sheharyar Ashraf, Namra Asif, Mohammad Asim, Jean Baptiste Assie, Amirul Asyraf, Anika Atique, AM Udara Lakshan Attanyake, Johann Auchabie, Christelle Chantalat Auger, Hugues Aumaitre, Adrien Auvet, Laurène Azemar, Cecile Azoulay, Benjamin Bach, Delphine Bachelet, Claudine Badr, Nadia Baig, J. Kenneth Baillie, Erica Bak, Agamemnon Bakakos, Nazreen Abu Bakar, Andriy Bal, Mohanaprasanth Balakrishnan, Valeria Balan, Pablo Serrano Balazote, Irene Bandoh, Bruno Sarmento Banheiro, Firouzé Bani-Sadr, Renata Barbalho, Wendy S. Barclay, Saef Umar Barnett, Michaela Barnikel, Helena Barrasa, Audrey Barrelet, Cleide Barrigoto, Noelia García Barrio, Marie Bartoli, Joaquín Baruch, Mustehan Bashir, Romain

Basmaci, Muhammad Fadhli Hassin Basri, Gianluigi Li Bassi, Denise Battaglini, Jules Bauer, Abigail Beane, Alexandra Bedossa, Ama Kwakyewaa Bedu-Addo, Ker Hong Bee, Husna Begum, Sylvie Behilill, Albertus Beishuizen, Gry Kloumann Bekken, Aleksandr Beljantsev, David Bellemare, Anna Beltrame, Beatriz Amorim Beltrão, Marine Beluze, Nicolas Benech, Lionel Eric Benjiman, Dehbia Benkerrou, Suzanne Bennett, Binny Benny, Luís Bento, Jan-Erik Berdal, Marcel van den Berge, Delphine Bergeaud, Hazel Bergin, Carlos Lumbreras Bermejo, Juan Luis Cruz Bermúdez, Giulia Bertoli, Lorenzo Bertolino, Simon Bessis, Sybille Bevilcaqua, Karine Bezulier, Amar Bhatt, Krishna Bhavsar, Claudia Bianco, Farah Nadiah Bidin, Clément Le Bihan, Zeno Bisoffi, François Bissuel, Patrick Biston, Laurent Bitker, Pablo Blanco-Schweizer, Catherine Blier, Frank Bloos, Mathieu Blot, Lucille Blumberg, Filomena Boccia, Laetitia Bodenes, Debby Bogaert, Anne-Hélène Boivin, Isabela Bolaños, Pierre-Adrien Bolze, François Bompart, Joe Bonney, Diogo Borges, Raphaël Borie, Elisabeth Botelho-Nevers, Lila Bouadma, Olivier Bouchaud, Sabelline Bouchez, Dounia Bouhmani, Damien Bouhour, Kévin Bouiller, Laurence Bouillet, Camile Bouisse, Anne-Sophie Boureau, John Bourke, Maude Bouscambert, Aurore Bousquet, Jason Bouziotis, Bianca Boxma, Marielle Boyer-Besseyre, Maria Boylan, Fernando Augusto Bozza, Axelle Braconnier, Cynthia Braga, Luca Brazzi, Dorothy Breen, Patrick Breen, David Brewster, Kathy Brickell, Fionnuala O Brien, Cyril Le Bris, Carlos Alexandre Antunes de Brito, Shaunagh Browne, Marjolein Brusse-Keizer, Nina Buchtele, Marielle Buisson, Erlina Burhan, Aidan Burrell, Ingrid G. Bustos, André Cabie, Susana Cabral, Joana Alves Cabrita, Eder Caceres, Cyril Cadoz, Annmarie O Callaghan, Guillermo Maestro de la Calle, Kate Calligy, Jose Andres Calvache, João Camões, Valentine Campana, Paul Campbell, Cecilia Canepa, Mireia Cantero, Pauline Caraux-Paz, Chiara Simona Cardellino, Filipa Cardoso, Filipe Cardoso, Nelson Cardoso, Sofia Cardoso, Simone Carelli, Nicolas Carlier, Thierry Carmoi, Gayle Carney, Inês Carqueja, Marie-Christine Carret, François Martin Carrier, Ida Carroll, Gail Carson, Maire-Laure Casanova, Mariana Cascão, Siobhan Casey, José Casimiro, Bailey Cassandra, Silvia Castañeda, Nidyanara Castanheira, Guylaine Castor-Alexandre, Ivo Castro, Maisa Guimarães de Castro, Ana Catarino, François-Xavier Catherine, Paolo Cattaneo, Roberta Cavalin, Giulio Giovanni Cavalli, Alexandros Cavayas, Adrian Ceccato, Lina Morales Cely, Minerva Cervantes-Gonzalez, Anissa Chair, Catherine Chakveatze, Adrienne Chan, Meera Chand, Jean-Marc Chapplain, Charlotte Charpentier, Julie Chas, Mobin Chaudry, Anjellica Chen, Yih-Sharng Chen, Léo Chenard, Matthew Pellan Cheng, Antoine Cheret, Jack Song Chia, Thibault Chiarabini, Julian Chica, Catherine Chirouze, Davide Chiumello, Sung-Min Cho, Orna Ni Choileain, Bernard Cholley, Marie-Charlotte Chopin, Ting Soo Chow, Jonathan Chua, Jose Pedro Cidade, Barbara Wanjiru Citarella, Anna Ciullo, Jennifer Clarke, Sara Clohisey, Cassidy Codan, Caitriona Cody, Alexandra Coelho, Jennifer Coles, Megan Coles, Gwenhaël Colin, Michael Collins, Sebastiano Maria Colombo, Pamela Combs, Marie Connor, Anne Conrad, Elaine Conway, Graham S. Cooke, Mary Copland, Hugues Cordel, Amanda Corley, Sabine Cornelis, Alexander Daniel Cornet, Arianne Joy Corpuz, Grégory Corvaisier, Camille Couffignal, Sandrine Couffin-Cadiergues, Roxane Courtois, Stéphanie Cousse, Sabine Croonen, Gloria Crowl, Jonathan Crump, Claudina Cruz, Marc Csete, Ailbhe Cullen, Matthew Cummings, Ger Curley, Gerard Curley, Elodie Curlier, Colleen Curran, Paula Custodio, Al-Awwab Dabaliz, Andrew Dagens, Darren Dahly, Heidi Dalton, Jo Dalton, Seamus Daly, Juliana Damas, Nick Daneman, Corinne Daniel, Emmanuelle A Dankwa, Jorge Dantas, B. P. Sanka Ruwan Sri Darshana, David Dean, Alexa Debard, Marie-Pierre Debray, Nathalie DeCastro, William Dechert, Lauren Deconninck, Romain Decours, Eve Defous, Isabelle Delacroix, Eric Delaveuve, Karen Delavigne, Andrea Dell'Amore, Christelle Delmas, Pierre Delobel, Corine Delsing, Elisa Demonchy, Emmanuelle Denis, Dominique Deplanque, Pieter Depuydt, Mehul Desai, Diane Descamps, Mathilde Desvallées, Eglantine Ferrand Devouge, Santi Dewayanti, Pathik Dhanger, Alpha Diallo, Sylvain Diamantis, Juan Jose Diaz, Priscila Diaz, Rodrigo Diaz, Kévin Didier, Jean-Luc Diehl, Wim Dieperink, Jérôme Dimet, Vincent Dinot, Fara Diop, Alphonsine Diouf, Yael Dishon, Félix Djossou, Annemarie B. Docherty, Helen Doherty, Carmen Infante Dominguez, Arjen M Dondorp, Christl A. Donnelly, Maria Donnelly, Chloe Donohue, Sean Donohue, Yoann Donohue, Peter Doran, Céline Dorival, Eric D'Ortenzio, James Joshua Douglas, Nathalie Dournon, Denisse Bazan Dow, Triona Downer, Joanne Downey, Mark Downing, Tom Drake, Aoife Driscoll, Murray Dryden, Vincent Dubee, François Dubos, Alexandre Ducancelle, Susanne Dudman, Paul Dunand, Jake Dunning, Mathilde Duplaix, Emanuele Durante-Mangoni, Bertrand Dussol, Juliette Duthoit, Xavier Duval, Anne Margarita Dyrhol-Riise, Sim Choon Ean, Marco Echeverria-Villalobos, Siobhan Egan, Carla Eira, Subbarao Elapavaluru, Brigitte Elharrar, Jacobien Ellerbroek, Philippine Eloy, Tarek Elshazly, Isabelle Enderle, Tomoyuki Endo, Chan Chee Eng, Ilka Engelmann, Vincent Enouf, Olivier Epaulard, Martina Escher, Mariano Esperatti, Hélène Esperou, Marina Esposito-Farese, Lorinda Essuman, João Estevão, Manuel Etienne, Nadia Ettalhaoui, Anna Greti Everding, Mirjam Evers, Isabelle Fabre, Marc Fabre, Amna Faheem, Arabella Fahy, Cameron J. Fairfield, Zul Fakar, Georges Le Falher, Komal Fareed, Pedro Faria, Ahmed Farooq, Hanan Fateena, Arie Zainul Fatoni, Karine Faure, Raphaël Favory, Mohamed Fayed, Niamh Feely, Laura Feeney, Jorge Fernandes, Marília Andreia Fernandes, Susana Fernandes, François-Xavier Ferrand, Joana Ferrão, Mário Ferraz, Benigno Ferreira, Bernardo Ferreira, Isabel Ferreira, Sílvia Ferreira, Nicolas Ferriere, Lucie Le Fevre, Céline Ficko, Claudia Figueiredo-Mello, Ana da Silva Filipe, Juan Fiorda, Thomas Flament, Clara Flateau, Tom Fletcher, Aline-Marie Florence, Letizia Lucia Florio, Deirdre Flynn, Claire Foley, Jean Foley, Claudio Duarte Fonseca, Tatiana Fonseca, Paa Kobina Forson, Simon Forsyth, Denise Foster, Giuseppe Foti, Erwan Fourn, Robert A. Fowler, Marianne Fraher, Rafael Freitas de Oliveira França, Diego Franch-Llasat, Christophe Fraser, John F Fraser, Marcela Vieira Freire, Ricardo Fritz, Stéphanie Fry, Nora Fuentes, Masahiro Fukuda, Argin G, Valérie Gaborieau, Rostane Gaci, Massimo Gagliardi, Jean-Charles Gagnard, Amandine Gagneux-Brunon, Sérgio Gaião, Phil Gallagher, Carrol Gamble, Charlotte Salmon Gandonniere, Yasmin Gani, Arthur Garan, Rui Caetano Garcês, Rebekha Garcia, Ruth N. Jorge García, Esteban Garcia-Gallo, Navya Garimella, Denis Garot, Valérie Garrait, Basanta Gauli, Nathalie Gault, Aisling Gavin, Anatoliy Gavrylov, Alexandre Gaymard, Johannes Gebauer, Eva Geraud, Nuno Germano, Jade Ghosn, Marco Giani, Tristan Gigante, Morgane Gilg, Elaine Gilroy, Guillermo Giordano, Michelle Girvan, Valérie Gissot, Daniel Glikman, Eric Gnall, François Goehringer, Jean-Christophe Goffard, Jin Yi Goh, Jonathan Golob, Rui Gomes, Joan Gómez-Junyent, Marie Gominet, Bronner P. Gonçalves, Alicia Gonzalez, Víctor Quirós González, Patricia Gordon, Isabelle Gorenne, Laure Goubert, Cécile Goujard, Tiphaine Goulenok, Margarite Grable, Edward Wilson Grandin, Beathe Kiland Granerud, Pascal Granier, Giacomo Grasselli, Christopher A. Green, William Greenhalf, Segolène Greffe, Domenico Luca Grieco, Matthew Griffee, Fiona Griffiths, Albert Groenendijk, Heidi Gruner, Yusing Gu, Jérémie Guedj, Martin Guego, Dewi Guellec, Daniela Guerreiro, Romain Guery, Anne Guillaumot, Laurent Guilleminault, Thomas Guimard, Laura van Gulik, Marieke Haalboom, Daniel Haber, Hannah Habraken, Ali Hachemi, Nadir Hadri, Fakhir Haidri, Sheeba Hakak, Adam Hall, Matthew Hall, Sophie Halpin, Jawad Hameed, Ansley Hamer, Rebecca Hamidfar, Naomi Hammond, Terese Hammond, Lim Yuen Han, Rashan Haniffa, Kok Wei Hao, Hayley Hardwick, Ewen M. Harrison, Janet Harrison, Mohd Shahnaz Hasan, Junaid Hashmi, Madiha Hashmi, Jarne Van Hattem, Muhammad Hayat, Ailbhe Hayes, Leanne Hays, Jan Heerman, Lars Heggelund, Ross Hendry, Martina Hennessy, Aquiles Henriquez-Trujillo, Maxime Hentzien, Diana Hernandez, Daniel Herr, José Miguel Cisneros Herreros, Andrew Hershey, Liv Hesstvedt, Dawn Higgins, Eibhlin Higgins, Rupert Higgins, Rita Hinchion, Nicholas Yee Liang Hing, Quentin Le Hingrat, Samuel Hinton, Hikombo Hitoto, Antonia Ho, Yi Bin Ho, Alexandre Hoctin, Isabelle Hoffmann, Wei Han Hoh, Oscar Hoiting, Rebecca Holt, Aleksander Rygh Holten, Jan Cato Holter, Peter Horby, Juan Pablo Horcajada, Koji Hoshino, Ikram Houas, Catherine L. Hough, Ali Ait Hssain, Jimmy Ming-Yang Hsu, Jean-

Sébastien Hulot, Felwa Bin Humaid, Abby Hurd, Iqbal Hussain, Lucian Durham III, Samreen Ijaz, Arfan Ikram, Hajnal-Gabriela Illes, Patrick Imbert, Mohammad Imran, Aftab Imtiaz, Hugo Inácio, Yun Sii Ing, Jonathan Samuel Chávez Iñiguez, Sarah Isgett, Tiago Isidoro, Nadiah Ismail, Margaux Isnard, Asami Ito, Daniel Ivulich, Danielle Jaafar, Salma Jaafoura, Julien Jabot, Clare Jackson, Nina Jamieson, Pierre Jaquet, Waasila Jassat, Coline Jaud-Fischer, Stéphane Jaureguiberry, Florence Jego, Anilawati Mat Jelani, Synne Jenum, Ruth Jimbo-Sotomayor, Miguel Pedrera Jiménez, Ong Yiaw Joe, Cédric Joseph, Mark Joseph, Mercé Jourdain, Roberto Roncon-Albuquerque Jr., Anna Jung, Dafsah Juzar, Ouifiya Kafif, Florentia Kaguelidou, Neerusha Kaisbain, Thavamany Kaleesvran, Sabina Kali, Smaragdi Kalomoiri, Muhammad Aisar Ayadi Kamaluddin, Zul Amali Che Kamaruddin, Mohd Nazlin Bin Kamarudin, Nadiah Kamarudin, Kavita Kamineni, Darshana Hewa Kandamby, Chris Kandel, Kong Yeow Kang, Darakhshan Kanwal, Pratap Karpayah, Christiana Kartsonaki, Anant Kataria, Kevin Katz, Christy Kay, Hannah Keane, Seán Keating, Andrea Kelly, Aoife Kelly, Claire Kelly, Niamh Kelly, Sadie Kelly, Yvelynne Kelly, Maeve Kelsey, Kalynn Kennon, Maeve Kernan, Younes Kerroumi, Sharma Keshav, Imrana Khalid, Osama Khalid, Antoine Khalil, Coralie Khan, Irfan Khan, Quratul Ain Khan, Rashid Nasim Khan, Sushil Khanal, Abid Khatak, Amin Khawaja, Michelle E Kho, Denisa Khoo, Ryan Khoo, Saye Khoo, Nasir Khoso, Khor How Kiat, Yuri Kida, Peter Kiiza, Antoine Kimmoun, Nobuya Kitamura, Paul Klenerman, Rob Klont, Stephen R Knight, Chamira Kodippily, Sabin Koirala, Caroline Kosgei, Arsène Kpangon, Karolina Krawczyk, Vinothini Krishnan, Oksana Kruglova, Deepali Kumar, Ganesh Kumar, Mukesh Kumar, Dinesh Kuriakose, Ethan Kurtzman, Neurinda Permata Kusumastuti, Demetrios Kutsogiannis, Galyna Kutsyna, Konstantinos Kyriakoulis, Marie Lachatre, Marie Lacoste, John G. Laffey, Nadhem Lafhej, Marie Lagrange, Fabrice Laine, Olivier Lairez, Sanjay Lakhey, Antonio Lalueza, Marc Lambert, Marie Langelot-Richard, Vincent Langlois, Eka Yudha Lantang, Marina Lanza, Cédric Laouénan, Samira Laribi, Delphine Lariviere, Stéphane Lasry, Naveed Latif, Odile Launay, Didier Laureillard, Yoan Lavie-Badie, Andrew Law, Andy Law, Teresa Lawrence, Minh Le, Niamh Ni Leathlobhair, Biing Horng Lee, Heng Gee Lee, James Lee, Jennifer Lee, Su Hwan Lee, Todd C. Lee, Yi Lin Lee, Gary Leeming, Bénédicte Lefebvre, Laurent Lefebvre, Benjamin Lefèvre, Sylvie LeGac, Jean-Daniel Lelievre, François Lellouche, Adrien Lemaignen, Véronique Lemee, Anthony Lemeur, Gretchen Lemmink, Ha Sha Lene, Marc Leone, Michela Leone, Quentin Lepiller, François-Xavier Lescure, Olivier Lesens, Mathieu Lesouhaitier, Amy Lester-Grant, Sophie Letrou, Bruno Levy, Yves Levy, Claire Levy-Marchal, Katarzyna Lewandowska, Erwan L'Her, Ali Liaquat, Geoffrey Liegeon, Kah Chuan Lim, Wei Shen Lim, Chantre Lima, Bruno Lina, Lim Lina, Andreas Lind, Guillaume Lingas, Sylvie Lion-Daolio, Keibun Liu, Marine Livrozet, Patricia Lizotte, Antonio Loforte, Navy Lolong, Leong Chee Loon, Diogo Lopes, Anthony L. Loschner, Paul Loubet, Bouchra Loufti, Gillian de Loughry, Guillame Louis, Silvia Lourenco, Lara Lovelace-Macon, Lee Lee Low, Marije Lowik, Jia Shyi Loy, Jean Christophe Lucet, Carlos *M. Luna*, Liem Luong, Nestor Luque, Dominique Luton, Nilar Lwin, Ruth Lyons, Olavi Maasikas, Oryane Mabiala, Moïse Machado, Sara Machado, Gabriel Macheda, Hashmi Madiha, Rafael Mahieu, Sophie Mahy, Ana Raquel Maia, Lars S. Maier, Mylène Maillet, Thomas Maitre, Ceila Maria Sant'Ana Malaque, Maximilian Malfertheiner, Nadia Malik, Paddy Mallon, Denis Malvy, Victoria Manda, Laurent Mandelbrot, Julie Mankikian, Edmund Manning, Aldric Manuel, Marion Le Maréchal, Flávio Marino, Samuel Markowicz, Ana Marques, Brian Marsh, Megan Marshal, John Marshall, Celina Turchi Martelli, Emily Martin, Guillaume Martin-Blondel, Ignacio Martin-Loeches, F. Eduardo Martinez, Martin Martinot, Ana Martins, João Martins, Nuno Martins, Gennaro Martucci, Olga Martynenko, Eva Miranda Marwali, Marsilla Marzukie, David Maslove, Phillip Mason, Sabina Mason, Sobia Masood, Moshe Matan, Meghena Mathew, Daniel Mathieu, Mathieu Mattei, Laurence Maulin, Michael Maxwell, Javier Maynar, Thierry Mazzoni, Colin McArthur, Peter McCanny, Aine McCarthy, Anne McCarthy, Colin McCloskey, Rachael McConnochie, Sherry McDermott, Sarah E. McDonald, Aine McElroy, Samuel McElwee, Victoria McEneany, Natalie McEvoy, Allison McGeer, Chris McKay, Johnny McKeown, Kenneth A. McLean, Bairbre McNicholas, Elaine McPartlan, Edel Meaney, Cécile Mear-Passard, Maggie Mechlin, Maqsood Meher, Ferruccio Mele, Luis Melo, Kashif Memon, Joao Joao Mendes, Diego de Mendoza, France Mentré, Alexander J. Mentzer, Emmanuelle Mercier, Noémie Mercier, Antoine Merckx, Mayka Mergeay-Fabre, Blake Mergler, Laura Merson, António Mesquita, Soizic Le Mestre, Osama Metwally, Agnès Meybeck, Dan Meyer, Alison M. Meynert, Vanina Meysonnier, Amina Meziane, Mehdi Mezidi, Céline Michelanglei, Isabelle Michelet, Vladislav Mihnovits, Jennene Miller, Hugo Miranda-Maldonado, Nor Arisah Misnan, Gwenaël Le Moal, Nik Nur Eliza Mohamed, Tahira Jamal Mohamed, Nassima Si Mohammed, Farah Nadia Mohd-Hanafiah, Asma Moin, Vincent Le Moing, Elena Molinos, Brenda Molloy, Mary Mone, Agostinho Monteiro, Filipa Brás Monteiro, Claudia Montes, Etienne De Montmollin, Giorgia Montrucchio, Sarah Moore, Shona C. Moore, Louis Gerbaud Morlaes, Lucia Moro, Catherine Motherway, Ana Motos, Hugo Mouquet, Julien Moyet, Caroline Mudara, Aisha Kalsoom Mufti, Ng Yong Muh, Dzawani Muhamad, Jimmy Mullaert, Fredrik Müller, Karl Erik Müller, Syed Muneeb, Nadeem Munir, Laveena Munshi, Aisling Murphy, Lorna Murphy, Marlène Murris, Srinivas Murthy, Himed Musaab, Himasha Muvindi, Gugapriyaa Muyandy, Dimitra Melia Myrodia, Hervé Le Nagard, Dave Nagpal, Alex Nagrebetsky, Nageswaran Narayanan, Alasdair Nazerali-Maitland, Nadège Neant, Ary Serpa Neto, Raul Neto, Carolien van Netten, Emily Neumann, Pauline Yeung Ng, Wing Yiu Ng, Anthony Nghi, Duc Nguyen, Alistair D Nichol, Prompak Nitayavardhana, Stephanie Nonas, Nurul Amani Mohd Noordin, Basri Mat Nor, Marion Noret, Nurul Faten Izzati Norharizam, Lisa Norman, Mahdad Noursadeghi, Adam Nowinski, Saad Nseir, Jose I Nunez, Elsa Nyamankolly, Annmarie O'Callaghan, Giovanna Occhipinti, Derbrenn OConnor, Max O'Donnell, Tawnya Ogston, Takayuki Ogura, Sophie O'Halloran, Ana Isabel de Pinho Oliveira, João Oliveira, Larissa Oliveira, Piero L. Olliaro, David S.Y. Ong, Jee Yan Ong, Wilna Oosthuyzen, Anne Opavsky, Peter Openshaw, Saijad Orakzai, Claudia Milena Orozco-Chamorro, Jamel Ortoleva, Javier Osatnik, Linda O'Shea, Miriam O'Sullivan, Siti Zubaidah Othman, Nadia Ouamara, Rachida Ouissa, Eric Oziol, Maïder Pagadoy, Justine Pages, Amanda Palacios, Job van der Palen, Massimo Palmarini, Giovanna Panarello, Prasan Kumar Panda, Hem Paneru, Lai Hui Pang, Mauro Panigada, Nathalie Pansu, Aurélie Papadopoulos, Rachael Parke, Taha Pasha, Jérémie Pasquier, Bruno Pastene, Fabian Patauner, Luís Patrão, Patricia Patricio, Juliette Patrier, Lisa Patterson, Rajyabardhan Pattnaik, Christelle Paul, Mical Paul, Jorge Paulos, William A. Paxton, Jean-François Payen, Sandra L Peake, Florent Peelman, Nathan Peiffer-Smadja, Vincent Peigne, Mare Pejkovska, Paolo Pelosi, Ithan D. Peltan, Rui Pereira, Daniel Perez, Luis Periel, Thomas Perpoint, Clara Mouton Perrot, Antonio Pesenti, Vincent Pestre, Michele Petrovic, Ventzislava Petrov-Sanchez, Frank Olav Pettersen, Gilles Peytavin, Scott Pharand, Michael Piagnerelli, Walter Picard, Olivier Picone, Carola Pierobon, Djura Piersma, Carlos Pimentel, Valentine Piquard, Catarina Pires, Isabelle Pironneau, Lionel Piroth, Chiara Piubelli, Riinu Pius, Laurent Plantier, Hon Shen Png, Julien Poissy, Ryadh Pokeerbux, Sergio Poli, Georgios Pollakis, Diane Ponscarme, Diego Bastos Porto, Andra-Maris Post, Douwe F. Postma, Pedro Povoa, Diana Póvoas, Jeff Powis, Sofia Prapa, Sébastien Preau, Christian Prebensen, Jean-Charles Preiser, Anton Prinssen, Mark G. Pritchard, Gamage Dona Dilanthi Priyadarshani, Lucia Proença, Sravya Pudota, Oriane Puéchal, Mathew Pulicken, Gregory Purcell, Eman Al Qasim, Luisa Quesada, Else Quist-Paulsen, Mohammed Quraishi, Christian Rabaud, Ebenezer Rabindrarajan, Aldo Rafael, Marie Rafiq, Ahmad Kashfi Haji Ab Rahman, Rozanah Abd Rahman, Arsalan Rahutullah, Fernando Rainieri, Giri Shan Rajahram, Pratheema Ramachandran, Nagarajan Ramakrishnan, José Ramalho, Ahmad Afiq Ramli, Blandine Rammaert, Grazielle Viana Ramos, Asim Rana, Rajavardhan Rangappa, Ritika Ranjan, Christophe Rapp, Aasiyah Rashan, Thalha Rashan, Ghulam Rasheed, Menaldi Rasmin, Indrek Rätsep, Tharmini Ravi, Ali Raza,

Andre Real, Stanislas Rebaudet, Sarah Redl, Brenda Reeve, Caroline Martins Rego, Attaur Rehman, Liadain Reid, Dag Henrik Reikvam, Renato Reis, Jordi Rello, Martine Remy, Hongru Ren, Anne-Sophie Resseguier, Matthieu Revest, Oleksa Rewa, Luis Felipe Reyes, Tiago Reyes, Ana Freitas Ribeiro, Maria Ines Ribeiro, David Richardson, Denise Richardson, Laurent Richier, Siti Nurul Atikah Ahmad Ridzuan, Diego Fernando Bautista Rincon, Ana L Rios, Asgar Rishu, Patrick Rispal, Karine Risso, Nicholas Rizer, Chiara Robba, André Roberto, David L. Robertson, Olivier Robineau, Ferran Roche-Campo, Paola Rodari, Simão Rodeia, Bernhard Roessler, Pierre-Marie Roger, Amanda Rojek, Jaime Cruz Rojo, Juliette Romaru, Mélanie Roriz, Rosanna De Rosa, Manuel Rosa-Calatrava, Michael Rose, Dorothea Rosenberger, Andrea Rossanese, Matteo Rossetti, Bénédicte Rossignol, Patrick Rossignol, Stella Rousset, Carine Roy, Benoît Roze, Clark D. Russell, Maeve Ryan, Maria Ryan, Steffi Ryckaert, Isabela Saba, Sairah Sadaf, Musharaf Sadat, Valla Sahraei, Nadia Saidani, Maximilien Saint-Gilles, Pranya Sakiyalak, Nawal Salahuddin, Leonardo Salazar, Jodat Saleem, Gabriele Sales, Stéphane Sallaberry, Hélène Salvator, Olivier Sanchez, Angel Sanchez-Miralles, Vanessa Sancho-Shimizu, Gyan Sandhu, Zulfiqar Sandhu, Pierre-François Sandrine, Oana Sandulescu, Mohammed El Sanharawi, Catarina Espírito Santo, Marlene Santos, Shirley Sarfo-Mensah, Benjamine Sarton, Sree Satyapriya, Rumaisah Satyawati, Egle Saviciute, Yen Tsen Saw, Tjard Schermer, Arnaud Scherpereel, Marion Schneider, Stephan Schroll, Michael Schwameis, Janet T. Scott, James Scott-Brown, Nicholas Sedillot, Tamara Seitz, Jaganathan Selvanayagam, Mageswari Selvarajoo, Caroline Semaille, Bambang Pujo Semedi, Malcolm G. Semple, Rasidah Bt Senian, Eric Senneville, Claudia Sepulveda, Filipa Sequeira, Tânia Sequeira, Ellen Shadowitz, Naseem Ali Shah, Syamin Asyraf Shahidan, Mohammad Shamsah, Shaikh Sharjeel, Pratima Sharma, Catherine A. Shaw, Victoria Shaw, Naseem Ali Sheikh, Dr. Rajesh Mohan Shetty, Haixia Shi, Mohiuddin Shiekh, Takuya Shiga, Hiroaki Shimizu, Keiki Shimizu, Sally Shrapnel, Pramesh Sundar Shrestha, Shubha Kalyan Shrestha, Wan Fadzlina Wan Muhd Shukeri, Hoi Ping Shum, Ng Yong Siang, Moses Siaw-Frimpong, Jeanne Sibiude, Atif Siddiqui, Louise Sigfrid, Rana Imran Sikander, Piret Sillaots, Catarina Silva, Fernanda Dias Da Silva, Maria Joao Silva, Rogério Silva, Thushan de Silva, Charlene Da Silveira, Wai Ching Sin, Budha Charan Singh, Moirangthem Bikram Singh, Punam Singh, Pompini Agustina Sitompul, Karisha Sivam, Linda Gail Skeie, Sue Smith, Benjamin Smood, Coilin Smyth, Michelle Smyth, Morgane Snacken, Dominic So, José Luis Bernal Sobrino, Tze Vee Soh, Joshua Solomon, Tom Solomon, Emily Somers, Agnès Sommet, Myung Jin Song, Rima Song, Tae Song, Azlan Mat Soom, Albert Sotto, Edouard Soum, Ana Chora Sousa, Marta Sousa, Alexandra Sperry, Shiranee Sriskandan, Sarah Stabler, Thomas Staudinger, Stephanie-Susanne Stecher, Ymkje Stienstra, Birgitte Stiksrud, Eva Stolz, Amy Stone, Adrian Streinu-Cercel, Anca Streinu-Cercel, Ami Stuart, David Stuart, Richa Su, Gabriel Suen, Jacky Y. Suen, Asfia Sultana, Charlotte Summers, Dubravka Supic, Deepashankari Suppiah, Lisa Mc Sweeney, Sarah Syahrin, Konstantinos Syrigos, Jaques Sztajnbok, Konstanty Szuldrzynski, Shirin Tabrizi, Fabio S. Taccone, Lysa Tagherset, Shahdattul Mawarni Taib, Sara Taleb, Jelmer Talsma, Younes Ait Tamlihat, Maria Lawrensia Tampubolon, Kim Keat Tan, Yan Chyi Tan, Hiroyuki Tanaka, Huda Taqdees, Arshad Taqi, Coralie Tardivon, Pierre Tattevin, M Azhari Taufik, Hassan Tawfik, Richard S. Tedder, Tze Yuan Tee, João Teixeira, Sofia Tejada, Marie-Capucine Tellier, Sze Kye Teoh, François Téoulé, Pleun Terpstra, Olivier Terrier, Nicolas Terzi, Hubert Tessier-Grenier, Adrian Tey, Alif Adlan Mohd Thabit, Anand Thakur, Zhang Duan Tham, Suvintheran Thangavelu, Vincent Thibault, Simon-Djamel Thiberville, Benoît Thill, Jananee Thirumanickam, Leong Chin Tho, Shaun Thompson, David Thomson, Emma C. Thomson, Mathew Thorpe, Surain Raaj Thanga Thurai, Ryan S. Thwaites, Paul Tierney, Vadim Tieroshyn, Jean-François Timsit, Noémie Tissot, Jordan Zhien Yang Toh, Maria Toki, Kristian Tonby, Sia Loong Tonnii, Marta Torre, Antoni Torres, Hernando Torres-Zevallos, Michael Towers, Tony Trapani, Théo Trioux, Cécile Tromeur, Ioannis Trontzas, Tiffany Trouillon, Jeanne Truong, Christelle Tual, Sarah Tubiana, Helen Tuite, Alexis F. Turgeon; Jean-Marie Turmel, Paul Le Turnier, Lance C.W. Turtle, Pawel Twardowski, Makoto Uchiyama, PG Ishara Udayanga, Andrew Udy, Roman Ullrich, Alberto Uribe, Asad Usman, Maria Sousa Uva, Timothy M. Uyeki, Cristinava Vajdovics, Luís Val-Flores, Paul van der Valk, Amélie Valran, Noémie Vanel, Henk Vanoverschelde, Pooja Varghese, Shoban Raj Vasudayan, Charline Vauchy, Pavan Kumar Vecham, Ilonka van Veen, Shaminee Veeran, Aurélie Veislinger, Nicky Van Der Vekens, Stijn Van de Velde, Sebastian Vencken, Sara Ventura, Annelies Verbon, José Ernesto Vidal, César Vieira, Deepak Vijayan, Bharath Kumar Tirupakuzhi Vijayaraghavan, Joy Ann Villanueva, Judit Villar, Andrea Villoldo, Benoit Visseaux, Hannah Visser, Chiara Vitiello, Harald Vonkeman, Peter Van der Voort, Peter de Vries, Fanny Vuotto, Noor Hidayu Wahab, Suhaila Abdul Wahab, Nadirah Abdul Wahid, Chih-Hsien Wang, Steve Webb, Jia Wei, Tan Pei Wen, Sylvie Van Der Werf, Sanne Wesselius, T. Eoin West, Murray Wham, Bryan Whelan, Nicole White, Paul Henri Wicky, Aurélie Wiedemann, Surya Otto Wijaya, Patricia J Williams, Keith Wille, Suzette Willems, Virginie Williams, Evert-Jan Wils, Calvin Wong, Teck Fung Wong, Xin Ci Wong, Yew Sing Wong, Gan Ee Xian, Lim Saio Xian, Kuan Pei Xuan, Ioannis Xynogalas, Siti Rohani Binti Mohd Yakop, Elizabeth Yarad; Masaki Yamazaki, Yazdan Yazdanpanah, Cécile Yelnik, Chian Hui Yeoh, Stephanie Yerkovich, Toshiki Yokoyama, Hodane Yonis, Obada Yousif, Akram Zaaqoq, Marion Zabbe, Masliza Zahid, Maram Zahran, Nor Zaila Binti Zaidan, Maria Zambon, Miguel Zambrano, Alberto Zanella, Nurul Zaynah, Hiba Zayyad, Alexander Zoufaly, David Zucman.

Sources of funding

This work was made possible by the UK Foreign, Commonwealth and Development Office and Wellcome [215091/Z/18/Z, 222410/Z/21/Z, 225288/Z/22/Z and 220757/Z/20/Z]; the Bill & Melinda Gates Foundation [OPP1209135]; the philanthropic support of the donors to the University of Oxford's COVID-19 Research Response Fund (0009109); CIHR Coronavirus Rapid Research Funding Opportunity OV2170359 and the coordination in Canada by Sunnybrook Research Institute; endorsement of the Irish Critical Care- Clinical Trials Group, coordination in Ireland by the Irish Critical Care- Clinical Trials Network at University College Dublin and funding by the Health Research Board of Ireland [CTN-2014-12]; the COVID clinical management team, AIIMS, Rishikesh, India; the COVID-19 Clinical Management team, Manipal Hospital Whitefield, Bengaluru, India; Cambridge NIHR Biomedical Research Centre; the dedication and hard work of the Groote Schuur Hospital Covid ICU Team and supported by the Groote Schuur nursing and University of Cape Town registrar bodies coordinated by the Division of Critical Care at the University of Cape Town; the Liverpool School of Tropical Medicine and the University of Oxford; the dedication and hard work of the Norwegian SARS-CoV-2 study team and the Research Council of Norway grant no 312780, and a philanthropic donation from Vivaldi Invest A/S owned by Jon Stephenson von Tetzchner; Imperial NIHR Biomedical Research Centre; the Comprehensive Local Research Networks (CLRNs) of which PJMO is an NIHR Senior Investigator (NIHR201385); Innovative Medicines Initiative Joint Undertaking under Grant Agreement No. 115523 COMBACTE, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies, in-kind contribution; Stiftungsfonds zur Förderung der Bekämpfung der Tuberkulose und anderer Lungenkrankheiten of the City of Vienna, Project Number: APCOV22BGM; Italian Ministry of Health "Fondi Ricerca corrente–L1P6" to IRCCS Ospedale Sacro Cuore–Don Calabria; Australian Department of Health grant (3273191); Gender Equity Strategic Fund at University of Queensland, Artificial Intelligence for Pandemics (A14PAN) at University of Queensland, the Australian Research Council Centre of Excellence for Engineered Quantum Systems (EQUS, CE170100009), the Prince Charles Hospital Foundation, Australia; grants from Instituto de Salud Carlos III, Ministerio de Ciencia, Spain; Brazil, National Council for

Scientific and Technological Development Scholarship number 303953/2018–7; the Firland Foundation, Shoreline, Washington, USA; the French COVID cohort (NCT04262921) is sponsored by INSERM and is funded by the REACTing (REsearch & ACtion emergING infectious diseases) consortium and by a grant of the French Ministry of Health (PHRC n°20-0424); a grant from foundation Bevordering Onderzoek Franciscus; the South Eastern Norway Health Authority and the Research Council of Norway; Institute for Clinical Research (ICR), National Institutes of Health (NIH) supported by the Ministry of Health Malaysia; preparedness work conducted by the Short Period Incidence Study of Severe Acute Respiratory Infection; the U.S. DoD Armed Forces Health Surveillance Division, Global Emerging Infectious Diseases Branch to the U.S Naval Medical Research Unit No. TWO (NAMRU-2) (Work Unit #: P0153_21_N2). These authors would like to thank Vysnova Partners, Inc. for the management of this research project. The Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit is funded by the Wellcome Trust.

This work uses data provided by patients and collected by the NHS as part of their care and supports #DataSavesLives. The data used for this research were obtained from ISARIC4C. We are extremely grateful to the 2648 frontline NHS clinical and research staff and volunteer medical students who collected these data in challenging circumstances, and the generosity of the patients and their families for their individual contributions in these difficult times. The COVID-19 Clinical Information Network (CO-CIN) data was collated by ISARIC4C Investigators. Data and Material provision were supported by grants from the National Institute for Health Research (NIHR; award CO-CIN-01), the Medical Research Council (MRC; grant MC_PC_19059), and the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at the University of Liverpool in partnership with Public Health England (PHE), (award 200907), NIHR HPRU in Respiratory Infections at Imperial College London with PHE (award 200927), Liverpool Experimental Cancer Medicine Centre (grant C18616/A25153), NIHR Biomedical Research Centre at Imperial College London (award ISBRC-1215-20013), and NIHR Clinical Research Network providing infrastructure support. We also acknowledge the support of Jeremy J Farrar and Nahoko Shindo.

Availability of data and materials

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

CRediT authorship contribution statement

Luis Felipe Reyes: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Esteban Garcia-Gallo:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Srinivas Murthy:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Yuli V. Fuentes:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Cristian C. Serrano:** Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Elsa D. Ibáñez-Prada:** Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **James Lee:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Amanda Rojek:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Barbara Wanjiru Citarella:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Bronner P. Gonçalves:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jake Dunning:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Indrek Rätsep:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Andre Emilio Viñan-Garces:** Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Christiana Kartsonaki:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jordi Rello:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ignacio Martin-Loeches:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Manu Shankar-Hari:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Piero L. Olliaro:** Conceptualization, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Laura Merson:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Srinivas Murthy declares receiving salary support from the Health Research Foundation and Innovative Medicines Canada Chair in Pandemic Preparedness Research. Ignacio Martin-Loeches declared lectures for Gilead, Thermofisher, MSD; advisory board participation for Fresenius Kabi, Advanz Pharma, Gilead, Accelerate, and Merck; and consulting fees for Gilead outside of the submitted work. These sponsors have not involvement in this manuscript. All the other authors do not have conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154318.

References

[1] Simonetti O, Martini M, Armocida E. COVID-19 and Spanish flu-18: review of medical and social parallelisms between two global pandemics. J Prev Med Hyg 2021;62(3):E613–20.
[2] Quah P, Li A, Phua J. Mortality rates of patients with COVID-19 in the intensive care unit: a systematic review of the emerging literature. Crit Care 2020;24(1):285.
[3] Rodriguez A, Ruiz-Botella M, Martin-Loeches I, Jimenez Herrera M, Sole-Violan J, Gomez J, et al. Deploying unsupervised clustering analysis to derive clinical phenotypes and risk factors associated with mortality risk in 2022 critically ill patients with COVID-19 in Spain. Crit Care 2021;25(1):63.
[4] Ohsfeldt RL, Choong CK, Mc Collam PL, Abedtash H, Kelton KA, Burge R. Inpatient hospital costs for COVID-19 patients in the United States. Adv Ther 2021;38(11):5557–95.
[5] Ashraf UM, Abokor AA, Edwards JM, Waigi EW, Royfman RS, Hasan SA, et al. SARS-CoV-2, ACE2 expression, and systemic organ invasion. Physiol Genomics 2021;53(2):51–60.
[6] Winkler ES, Bailey AL, Kafai NM, Nair S, McCune BT, Yu J, et al. SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. Nat Immunol 2020;21(11):1327–35.
[7] Beyerstedt S, Casaro EB, Rangel EB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis 2021;40(5):905–19.
[8] Potere N, Valeriani E, Candeloro M, Tana M, Porreca E, Abbate A, et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Crit Care 2020;24(1):389.
[9] Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med 2020;38(7):1504–7.
[10] Linschoten M, Peters S, van Smeden M, Jewbali LS, Schaap J, Siebelink HM, et al. Cardiac complications in patients hospitalised with COVID-19. Eur Heart J Acute Cardiovasc Care 2020;9(8):817–23.
[11] Drake TM, Riad AM, Fairfield CJ, Egan C, Knight SR, Pius R, et al. Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO clinical characterisation protocol UK: a prospective, multicentre cohort study. Lancet 2021;398(10296):223–37.

[12] Africano HF, Serrano-Mayorga CC, Ramirez-Valbuena PC, Bustos IG, Bastidas A, Vargas HA, et al. Major adverse cardiovascular events during invasive pneumococcal disease are serotype dependent. Clin Infect Dis 2021;72(11):e711–9.
[13] Qureshi AI, Baskett WI, Huang W, Shyu D, Myers D, Raju M, et al. Acute ischemic stroke and COVID-19: an analysis of 27 676 patients. Stroke 2021;52(3):905–12.
[14] Cheng MP, Cau A, Lee TC, Brodie D, Slutsky A, Marshall J, et al. Acute cardiac injury in coronavirus disease 2019 and other viral infections-a systematic review and meta-analysis. Crit Care Med 2021;49(9):1558–66.
[15] Sluis WM, Linschoten M, Buijs JE, Biesbroek JM, den Hertog HM, Ribbers T, et al. Risk, clinical course, and outcome of ischemic stroke in patients hospitalized with COVID-19: a multicenter cohort study. Stroke 2021;52(12):3978–86.
[16] Labbe V, Ederhy S, Lapidus N, Salem JE, Trinh-Duc A, Cohen A, et al. Characterization and outcomes of acute myocardial injury in COVID-19 intensive care patients. Infection 2021;49(3):563–6.
[17] Jordaan P, Dumotier B, Traebert M, Miller PE, Ghetti A, Urban L, et al. Cardiotoxic potential of hydroxychloroquine, chloroquine and azithromycin in adult human primary cardiomyocytes. Toxicol Sci 2021;180(2):356–68.
[18] Ho TC, Wang YH, Chen YL, Tsai WC, Lee CH, Chuang KP, et al. Chloroquine and hydroxychloroquine: efficacy in the treatment of the COVID-19. Pathogens 2021; 10(2).
[19] Negrini F, de Sire A, Andrenelli E, Lazzarini SG, Patrini M, Ceravolo MG, et al. Rehabilitation and COVID-19: the cochrane rehabilitation 2020 rapid living systematic review. Update as of July 31st, 2020. Eur J Phys Rehabil Med 2020;56 (5):652–7.
[20] Birkhoelzer SM, Cowan E, Guha K. COVID-19: treatments and the potential for cardiotoxicity. Br J Cardiol 2021;28(1):7.
[21] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5(7):802–10.
[22] Rey JR, Caro-Codon J, Rosillo SO, Iniesta AM, Castrejon-Castrejon S, Marco-Clement I, et al. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. Eur J Heart Fail 2020;22(12):2205–15.
[23] Group ICC. The value of open-source clinical science in pandemic response: lessons from ISARIC. Lancet Infect Dis 2021;21(12):1623–4.
[24] Group ICC, Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, et al. ISARIC-COVID-19 dataset: a prospective, standardized, global dataset of patients hospitalized with COVID-19. Sci Data 2022;9(1):454.
[25] Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol 2021;21(1):241.
[26] Vukmir RB. Cardiac arrhythmia therapy. Am J Emerg Med 1995;13(4):459–70.
[27] Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 2021;1. S1071-9164(21)00050-6.
[28] Thygesen K, Alpert JS, White HD, Joint ESCAAHAWHFTFftRoMI. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50(22):2173–95.
[29] Chapman AR, Adamson PD, Mills NL. Assessment and classification of patients with myocardial injury and infarction in clinical practice. Heart 2017;103(1):10–8.
[30] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(7):2064–89.
[31] Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 2012;125(6): 773–81.
[32] Wiese AD, Mitchel E, Ndi D, Markus TM, Talbot HK, Schaffner W, et al. The risk of acute myocardial infarction among patients with laboratory-confirmed invasive pneumococcal disease: a self-controlled case series study. Clin Infect Dis 2023: ciad065.
[33] Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. Lancet Infect Dis 2009;9(10):601–10.
[34] Writing C, Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022;79(17): 1717–56.
[35] Pellicori P, Doolub G, Wong CM, Lee KS, Mangion K, Ahmad M, et al. COVID-19 and its cardiovascular effects: a systematic review of prevalence studies. Cochrane Database Syst Rev 2021;3:CD013879.
[36] Gu ZC, Zhang C, Kong LC, Shen L, Li Z, Ge H, et al. Incidence of myocardial injury in coronavirus disease 2019 (COVID-19): a pooled analysis of 7,679 patients from 53 studies. Cardiovasc Diagn Ther 2020;10(4):667–77.
[37] Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020; 191:148–50.
[38] Jone PN, John A, Oster ME, Allen K, Tremoulet AH, Saarel EV, et al. SARS-CoV-2 infection and associated cardiovascular manifestations and complications in children and young adults: a scientific statement from the American Heart Association. Circulation 2022;145(19):e1037–52.
[39] Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020;22. S0140-6736(20)31180-6.
[40] Tsiakos K, Tsakiris A, Tsibris G, Voutsinas PM, Panagopoulos P, Kosmidou M, et al. Early start of oral clarithromycin is associated with better outcome in COVID-19 of moderate severity: the ACHIEVE open-label single-arm trial. Infect Dis Ther 2021; 10(4):2333–51.
[41] Gyselinck I, Liesenborghs L, Belmans A, Engelen MM, Betrains A, Van Thillo Q, et al. Azithromycin for treatment of hospitalised COVID-19 patients: a randomised, multicentre, open-label clinical trial (DAWn-AZITHRO). ERJ Open Res 2022;8(1).
[42] Farmakis IT, Minopoulou I, Giannakoulas G, Boutou A. Cardiotoxicity of azithromycin in COVID-19: an overall proportion meta-analysis. Adv Respir Med 2022;90(3):171–82.
[43] Popp M, Stegemann M, Riemer M, Metzendorf MI, Romero CS, Mikolajewska A, et al. Antibiotics for the treatment of COVID-19. Cochrane Database Syst Rev 2021; 10:CD015025.
[44] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5(7):811–8.
[45] Kini A, Cao D, Nardin M, Sartori S, Zhang Z, Pivato CA, et al. Types of myocardial injury and mid-term outcomes in patients with COVID-19. Eur Heart J Qual Care Clin Outcomes 2021;7(5):438–46.
[46] Kim YE, Huh K, Park YJ, Peck KR, Jung J. Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19 infection. JAMA 2022;328(9):887–9.