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Cardiovascular events after COVID-19 hospitalization: long-term follow-up

Eventos cardiovasculares tras la hospitalización por COVID-19: seguimiento a largo plazo

To the Editor,

Multiple deleterious cardiovascular effects produced by coronavirus disease 2019 (COVID-19) have been reported, affecting both the heart and the systemic vascular endothelium.[1,2] This is reflected by the frequent and varied cardiovascular manifestations described in the acute phase of the disease.[3,4] However, there are limited data on its manifestations in the mid- and long-term.

To analyze the cumulative incidence of major cardiovascular events (MACE) during the first year after hospitalization for COVID-19, we performed a prospective analysis of all patients discharged following COVID-19 hospitalization in a center of excellence between 10 March and May 4, 2020 and followed up until 18 April 2021. Patients were deemed to have COVID-19 on the basis of clinical signs and symptoms compatible with the disease and positive polymerase chain reaction for severe adult respiratory syndrome coronavirus type 2 (SARS-CoV-2).

MACE included acute coronary syndrome, cerebrovascular event, venous thromboembolic disease (VTED), hospitalization for heart failure, and cardiovascular death. Survival analysis was performed with a Kaplan-Meier model followed by Cox regression analysis that included the variables with a heterogeneous distribution between the groups with and without events to analyze the factors associated with events. The study was approved by a research ethics committee, who waived the need to obtain informed consent in light of the ongoing epidemic.

The analysis included 673 patients (53.9% men; mean age, 66.7 ± 15.8 years). The prevalence of cardiovascular risk factors was high: 17.9% were smokers, 30.3% had diabetes, and 20.8% were obese. Among the different comorbidities analyzed, the most prevalent were cardiac comorbidities (23.1%).

The baseline population characteristics and the main details of the COVID-19 hospital admissions are reported in table 1.

Most of the patients were symptomatic for at least 1 week before their admission (56.2%), and the most common radiological pattern was bilateral consolidation (72.6%). During hospital stay, most of the patients had some degree of acute dyspnea, although only 2.4% required invasive mechanical ventilation. All patients received some form of treatment for the infection, the most common being hydroxychloroquine (93.3%). The mean hospital stay was 9.3 ± 6.2 days.

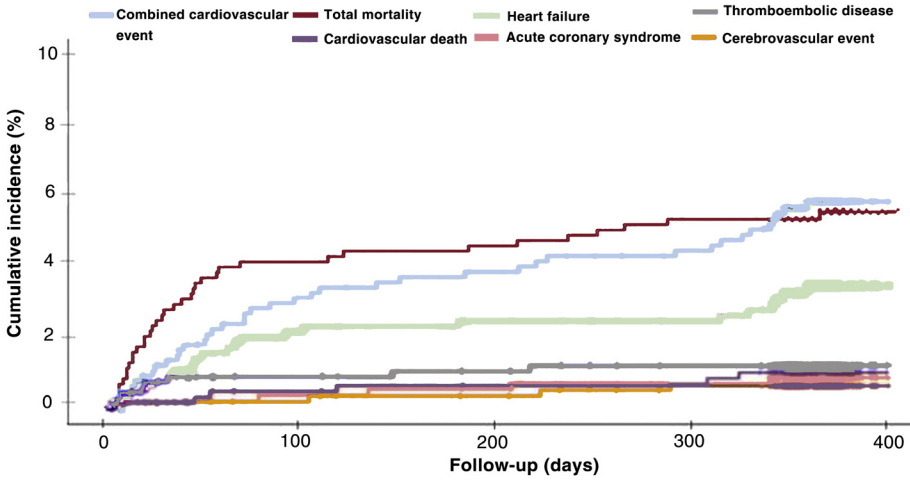
Table 1
Population characteristics

	Whole population (n = 673)	Patients without combined event (n = 633)	Patients with combined event (n = 40)	*P*
Baseline characteristics				
Age, y	66.7 ± 15.8	66.2 ± 15.7	75.5 ± 15.0	< .001
Male sex	363 (53.9)	343 (54.2)	20 (50.0)	.606
Hypertension	363 (53.9)	338 (53.4)	25 (62.5)	.263
Diabetes mellitus	125 (18.6)	117 (18.5)	8 (20.0)	.815
Dyslipidemia	238 (35.4)	221 (34.9)	22 (42.1)	.330
Smoking	94 (14.0)	88 (13.9)	6 (15.0)	.846
Obesity	99 (14.7)	94 (14.9)	5 (12.5)	.681
Ischemic heart disease	52 (7.7)	45 (7.1)	7 (17.5)	.017
Heart failure	50 (7.4)	41 (6.5)	9 (22.5)	< .001
Atrial fibrillation	54 (8.0)	46 (7.3)	8 (20.0)	.004
Cerebrovascular disease	46 (6.5)	39 (6.2)	12 (17.5)	.022
Dementia	43 (6.4)	35 (5.5)	8 (20.0)	< .001
Liver disease	16 (2.4)	14 (2.2)	2 (5.0)	.264
Chronic kidney disease	54 (8.0)	47 (7.4)	7 (17.5)	.023
Renal replacement therapy	7 (1.1)	6 (1.0)	1 (2.5)	.451
Chronic obstructive pulmonary disease	39 (5.8)	31 (4.9)	8 (20.0)	< .001
Asthma	30 (4.5)	28 (4.4)	2 (4.8)	.864
OSAHS	42 (6.3)	41 (6.5)	1 (2.4)	.312
History of cancer	55 (8.1)	49 (7.8)	6 (14.0)	.266
Previous institutionalization	107 (15.9)	93 (14.7)	24 (35.0)	.001

Table 1 *(Continued)*
Population characteristics

	Whole population (n = 673)	Patients without combined event (n = 633)	Patients with combined event (n = 40)	*P*
Variables relating to COVID-19 admission				
Duration of symptoms before admission				.090
< 7 days	378 (56.2)	349 (66.5)	29 (71.8)	
> 7 days	280 (41.6)	269 (43.5)	11 (28.2)	
Unknown	15 (2.2)	15 (2.5)	0	
CURB-65 score	0.98 ± 0.9	0.88 ± 0.9	1.57 ± 0.8	.003
Radiological pattern				.356
No infiltrate	9 (1.3)	9 (1.4)	0	
Unilateral infiltrate	167 (24.8)	154 (25.6)	13 (35.1)	
Bilateral infiltrate	462 (68.6)	438 (72.8)	24 (64.9)	
Other	26 (3.8)	22 (2.2)	4 (11.7)	
ARDS during admission				.024
No	316 (47.4)	300 (49.1)	16 (29.1)	
Mild	21 (38.2)	157 (25.7)	21 (38.2)	
Moderate	17 (30.9)	133 (21.8)	17 (30.9)	
Severe	22 (3.3)	21 (3.4)	1 (1.8)	
Need for IMV	16 (2.4)	14 (2.3)	2 (3.7)	.522
Acute renal failure during admission	77 (11.5)	64 (10.4)	13 (23.6)	.003
Hospital stay, d	9.3 ± 6.2	9.2 ± 6.1	11.1 ± 6.7	.060

ARDS, adult respiratory distress syndrome; CURB-65, score based on the presence of confusion, blood urea level, respiratory rate, blood pressure, and age > 65 years; IMV, invasive mechanical ventilation; OSAHS, obstructive sleep apnea/hypopnea syndrome.
Values are expressed as No. (%) or mean ± standard deviation.



	Cumulative incidence (%)	Early events* (%)	Time to event (days)
Combined event (cardiovascular death, ACS, CVE, VTED or heart failure)	40 (5.9)	12 (30.0)	74.0 (26-274)
Cardiovascular death	5 (0.7)	1 (20.0)	52.0 (21-92)
ACS	5 (0.7)	1 (20.0)	135.0 (21-92)
CVE	6 (0.9)	1 (16.7)	257.5 (80-314)
VTED **- Deep vein thrombosis** **- Pulmonary thromboembolism**	8 (1.2) 3 (0.5) 5 (0.7)	6 (75.0) 1 (33.3) 5 (100.0)	18.5 (5-100) 146.0 (18-182) 7.0 (3-29)
Heart failure	22 (3.3)	6 (27.3)	64.0 (30-318)

Figure 1. Cumulative incidence of events during follow-up. ACS, acute coronary syndrome; CVE, cerebrovascular event; VTED, venous thromboembolic disease. * In the first 30 days after hospitalization. gr1.

After a follow-up of 352.2 ± 70.4 days, the combined event occurred in 40 patients (5.9%). One third of the events occurred during the first 30 days after hospital discharge, with a median time to first event of 74.0 [range, 26-274] days.

Independently, the most common cardiovascular event during follow-up was hospitalization for heart failure (3.3%), while 0.7% had acute coronary syndrome.

Although most of the events were late (more than 1 month after hospitalization), 75% of the cases of VTED occurred in the first 30 days, with a median time to event of 18.5 [5-100] days. Of note, 62.5% of the cases of VTED were pulmonary thromboembolisms, all of them occurring early after hospitalization, with a median 7.0 [3-29] days until the event.

Thirty-six patients (5.3%) died during follow-up, although cardiovascular mortality was low (0.7%). The events recorded during follow-up are shown in figure 1.

A history of dementia (hazard ratio = 3.06, 95% confidence interval, 1.16-8.08; $P = .024$) and history of chronic obstructive pulmonary disease (hazard ratio = 4.11; 95% confidence interval, 1.64-10.30; $P = .003$) were independently associated with the occurrence of the combined event.

The main finding was the increased incidence of cardiovascular events after hospitalization: 1 in every 16 patients hospitalized for COVID-19 had a MACE in the first year after admission and one third of these occurred during the first 30 days. Admission for heart failure was the most common event after COVID-19 admission, and VTED, particularly pulmonary embolism, was the earliest.

These data further highlight the association between COVID-19 and cardiovascular disease. Although further studies are needed to obtain more detail on the pathophysiological basis for this association, some studies have revealed a high prevalence of structural myocardial damage in the months following the infection.[5] In addition, the short time until the onset of VTED is in line with the existing evidence, which has described a high association of venous events in these patients.[6] These data lend plausibility to the hypothesis that SARS-CoV-2 acts as a modifying factor of cardiovascular disease, analogous to the interaction of other more studied agents such as the influenza virus. However, more detailed studies on the long-term cardiovascular effect of the virus are needed to allow characterization of the underlying pathophysiological mechanisms.

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AUTHORS' CONTRIBUTIONS

All authors made a substantial contribution to this manuscript, in terms of writing (M. Negreira-Caamaño; J. Piqueras-Flores), design (M. Negreira-Caamaño; J. Martínez-Del Río; D. Águila-Gordo; C. Mateo-Gómez), execution (M. Negreira-Caamaño; J. Martínez-Del Río; D. Águila-Gordo; C. Mateo-Gómez; M. Soto-Pérez; J. Piqueras-Flores), data collection (M. Negreira-Caamaño; J. Martínez-Del Río; D. Águila-Gordo; C. Mateo-Gómez; M. Soto-Pérez; J. Piqueras-Flores) and data analysis (M. Negreira-Caamaño; J. Martínez-Del Río; D. Águila-Gordo; C. Mateo-Gómez; D. Águila-Gordo).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in relation to the present study.

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