3. Petersen A, Bressem K, Albrecht J, et al. The role of visceral adiposity in the severity of COVID-19: Highlights from a unicenter cross-sectional pilot study in Germany. *Metabolism.* 2020;110:154317.
4. Kim IC, Han S. Epicardial adipose tissue: fuel for COVID-19-induced cardiac injury? *Eur Heart J.* 2020;41:2334–2335.
5. Malavazos AE, Goldberger JJ, Iacobellis G. Does epicardial fat contribute to COVID-19 myocardial inflammation? *Eur Heart J.* 2020;41:2333.
6. Hu H, Chung SA, Nayak KS, Jackson HA, Gilsanz V. Differential computed tomographic attenuation of metabolically active and inactive adipose tissues. *J Comput Assist Tomogr.* 2011;35:65–71.

https://doi.org/10.1016/j.rec.2021.07.006

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.

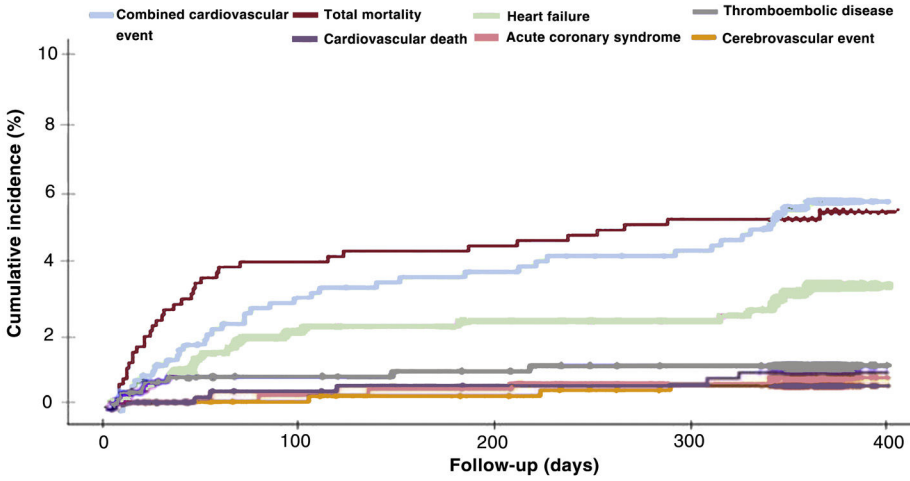
Table 1
Population characteristics

	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.

FUNDING

The authors declare that they have received no external funding for this study.

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.

Martín Negreira-Caamaño,[a,*] Jorge Martínez-Del Río,[a] Daniel Águila-Gordo,[a] Cristina Mateo-Gómez,[a] Maeve Soto-Pérez,[a] and Jesús Piqueras-Flores[a,b]

[a]*Servicio de Cardiología, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*
[b]*Facultad de Medicina, Universidad de Castilla La-Mancha, Ciudad Real, Spain*

[*] Corresponding author:
E-mail address: martin.negcam@gmail.com
(M. Negreira-Caamaño).

Available online 9 September 2021

REFERENCES

1. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. *Life Sci.* 2020;253:117723.
2. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5:811–818.
3. Shafi AMA, Shaikh SA, Shirke MM, Iddawela S, Harky A. Cardiac manifestations in COVID-19 patients—A systematic review. *J Card Surg.* 2020;35:1988–2008.
4. Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J.* 2020;41:1798–1800.
5. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5:1265–1273.
6. Suh YJ, Hong H, Ohana M, et al. Pulmonary embolism and deep vein thrombosis in COVID-19: a systematic review and meta-analysis. *Radiology.* 2021;298:E70–E80.

https://doi.org/10.1016/j.rec.2021.09.001