



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

José López-Fernández\*, Gabriel García Plaza  
e Ismael Antón Fernández

Servicio de Cirugía General y del Aparato Digestivo, Hospital  
Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria,  
España

\* Autor para correspondencia.  
Correo electrónico: [jlopezfdz89@gmail.com](mailto:jlopezfdz89@gmail.com) (J. López-Fernández).

<https://doi.org/10.1016/j.medcli.2021.03.018>  
0025-7753/ © 2021 Elsevier España, S.L.U. Todos los derechos reservados.

**Mid-term effects of SARS-CoV-2 infection on cardiovascular outcomes**



**Efectos cardiovasculares a medio plazo de la infección por SARS-CoV-2**

Dear Editor:

Coronavirus disease 2019 (COVID-19) has become the most important public health issue worldwide due to its rapid spread, morbidity, and mortality. Although its main target is the respiratory system, a significant proportion of COVID-19 patients exhibits myocardial injury, which is associated with a worse in-hospital prognosis.<sup>1-3</sup> The pathophysiological mechanisms related to cardiovascular affectation are not entirely understood but may be related to intense endothelial damage, inflammation, thrombosis, and coagulopathy.<sup>4</sup> However, it is unknown if COVID-19 may affect the mid and long-term cardiovascular outcomes. We aim to describe the cardiovascular outcomes at six months following COVID-19 diagnosis.

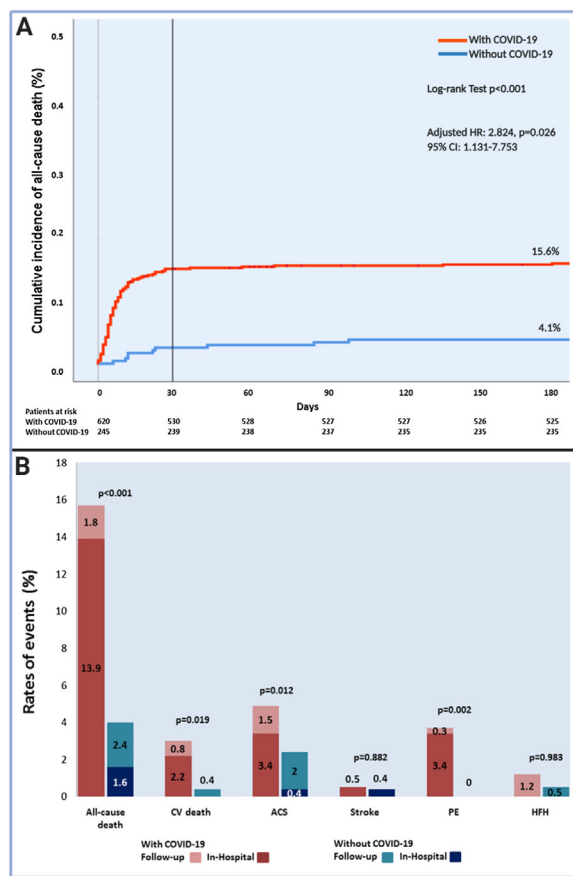
This is a single-center, retrospective registry of all consecutive hospitalized patients who underwent a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 from March 1 to April 19, 2020, at the University Hospital Hospital Clínic, Barcelona, Spain. The study was approved by the Ethics Committee and adhered to the principles outlined in Helsinki's Declaration.

All information was obtained from electronic records (medical history and national social security database). Patients were divided into two groups according to the RT-PCR result to have a comparator arm. Rates of all-cause death and cardiovascular outcomes (cardiovascular death, acute coronary syndrome [ACS], stroke, heart failure hospitalization [HFH], and pulmonary embolism [PE]) were evaluated at 6-month follow-up and compared between groups. Endpoints were defined according to the Academic Research Consortium-2.<sup>5</sup> A Cox proportional hazards model along with a Wald test was used for comparison of outcomes. A crude analysis was performed for all endpoints, and adjusted analysis was performed only for all-cause death. Kaplan-Meier curves were used to derive the event rates at follow-up and to plot time-to-event curves. Patients not eligible for six-month follow-up were considered at risk until the date of last follow-up, at which point they were censored. A two-side *p*-value <0.05 was considered statistically significant. All data were processed using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA).

A total of 865 individuals were included in the study, divided into 620 with COVID-19 and 245 without COVID-19. Patients with COVID-19 were older (59 ± 18.6 years vs. 45 ± 18.5 years, *p* < 0.001), more frequently male (333 [53.7%] vs. 112 [45.7%], *p* = 0.034), with higher body mass index (BMI) (27.5 ± 5.0 vs. 24.2 ± 5.0, *p* < 0.001) compared with patients without. Furthermore, patients with COVID-19 had higher rates of hypertension (237 [38.2%] vs. 43 [17.6%], *p* < 0.001), diabetes mellitus [94 (15.2%) vs. 6 (2.4%), *p* < 0.001], and hypercholesterolemia [161 (26%) vs. 23 (9.4%), *p* < 0.001] as compared to non-COVID-19 counterparts.

Patients with COVID-19 had a higher risk of all-cause death compared to those without (15.6% [97/620] vs. 4.1% [10/245], adjusted HR: 2.82, [95% CI: 1.13–7.75], *p* = 0.026) (Fig. 1A). Of note, this difference was driven by a higher risk of in-hospital all-cause death (13.9% vs. 1.6%, un-adjusted HR: 9.10 [95% CI 3.34–24.80], *p* = 0.001), with no differences in post-discharge risk of all-cause death between patients with or without COVID-19 (2.1% [11/534] vs. 2.5% [6/241], un-adjusted HR: 0.85 [95% CI 0.31–2.28], *p* = 0.739). Furthermore, at 6-month follow-up, cardiovascular death and PE rates were higher in COVID-19 patients than those without. Nevertheless, these differences were due to a higher rate of in-hospital cardiovascular death (2.3% vs. 0%, *p* = 0.018) and PE (3.4% vs. 0%; *p* = 0.001), without differences in the post-discharge follow-up. The in-hospital ACS rate was higher in patients with COVID-19 than those without (3.4% vs. 0.4%, *p* = 0.008). At 6-month, there were no differences in ACS between patients with or without COVID-19. Ultimately, there were no differences in stroke or HFH (Fig. 1B).

At 6-month follow-up, we found a higher risk of all-cause death in COVID-19 patients. However, the difference between the groups was driven by a higher in-hospital all-cause death risk, without



**Fig. 1.** All-cause death and cardiovascular outcomes at six months follow-up in patients with or without COVID-19. (A) All-cause death time-to-event curve. (B) Six months follow-up cardiovascular outcomes. ACS, acute coronary syndrome; CV, cardiovascular; HFH, heart failure hospitalization; PE, pulmonary embolism.

an increased risk during the post-discharge follow-up. Our data suggest that COVID-19 infection could be related to adverse acute cardiovascular outcomes without impaired outcomes beyond the disease's acute phase. Larger registries with extended follow-up must be performed to determine the long-term effect of COVID-19 on the cardiovascular system.

### Funding

This study has been funded by Carlos III Institute, Madrid, Spain [Research grant COV20/00040].

### Bibliografía

- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020;17:259–60, <http://dx.doi.org/10.1038/s41569-020-0360-5>.
- 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;5:802–10, <http://dx.doi.org/10.1001/jamacardio.2020.0950>.
- Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. *J Card Fail.* 2020;26:470–5, <http://dx.doi.org/10.1016/j.cardfail.2020.04.009>.

- Ortega-Paz L, Capodanno D, Montalescot G, Angiolillo DJ. Coronavirus disease 2019 – associated thrombosis and coagulopathy: review of the pathophysiological characteristics and implications for antithrombotic management. *J Am Heart Assoc.* 2021;10:1–24, <http://dx.doi.org/10.1161/JAHA.120.019650>.
- García-García HM, McFadden E, Farb A, Mehran R, Stone GW, Spertus J, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. *Circulation.* 2018;137:2635–50, <http://dx.doi.org/10.1161/CIRCULATIONAHA.117.029289>.

Victor Arévalos<sup>1</sup>, Luis Ortega-Paz<sup>1</sup>, Salvatore Brugaletta\*

*Clinic Cardiovascular Institute, Department of Cardiology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain*

\* Corresponding author.

E-mail address: [sabrugaletta@gmail.com](mailto:sabrugaletta@gmail.com) (S. Brugaletta).

<sup>1</sup> Both authors equally contributed to this paper.

<https://doi.org/10.1016/j.medcli.2021.05.006>

0025-7753/ © 2021 Elsevier España, S.L.U. All rights reserved.

## Belimumab in refractory systemic lupus erythematosus pleural effusion



### Utilidad de belimumab en derrame pleural secundario a lupus eritematoso sistémico refractario

Dear Editor,

We read with interest the publication in *Medicina Clínica* by Salman-Monte et al.<sup>1</sup> describing belimumab as a useful alternative therapy in systemic lupus erythematosus serositis (SLE). This research group have published satisfactory treatment response to belimumab for refractory pericarditis<sup>1</sup> and pleuritis<sup>2</sup> in SLE who fulfilled 1982 American College of Rheumatology criteria for SLE.<sup>3</sup> Mainly, SLE patients who develop refractory serositis may show short or long-standing SLE course. Several immunosuppressants (methotrexate, hydroxychloroquine, leflunomide along with low-medium prednisone dosage; and aspirin for the pericarditis SLE patient) were prescribed to control other than serositis symptoms. Since majority of these SLE features are frequent and mild, though, the need to control patients' serositis symptoms, short of breath and serositis severity (massive pleuritis) made the authors try belimumab in order to control disease activity. Despite patients had previously failed to control disease activity through several treatments, belimumab showed both rapid efficacy and safety. Within a span of 6 months, both patients showed significant clinical improvement with no SLE flares and prednisone dosage was lowered. Although several trials of belimumab have been performed in SLE, there is no specific data in serositis outcome, nor even in clinical practice.<sup>4</sup>

We present a 29-year old woman with established SLE diagnosed in April 2018 with following ACR SLE criteria: malar rash, oral ulcers, photosensitivity, positive antinuclear antibodies (ANA) (1/640 titer) and anti-dsDNA antibodies testing. The patient also showed Raynaud's phenomenon hypocomplementaemia, positive RNP and Sm antibodies testing and polyarthralgia and fatigue. Initially, the patient responded to low-dose prednisone and hydroxychloroquine therapy. Patient also suffered from mild allergic asthma. In September 2019 the patient showed short of breath, chest pain, non-productive cough and a massive left pleuritis in the X-ray testing with an exudative pleural effusion evidence after performing diagnostic thoracentesis. After com-

mon respiratory and systemic infections and malignant, metabolic, cardiac and renal conditions were ruled out, patient initiated high-prednisone dosage and mycophenolate mophetil 720 mg daily, alongside hydroxychloroquine. Despite observing a moderate response after eight months of treatment, a moderate right pleuritis image in the routinely X-ray testing was demonstrated, higher anti-dsDNA level and worse hypocomplementaemia were present. Therefore, we considered mycophenolate mophetil as insufficient to control SLE activity (SLEDAI = 8) and subcutaneous belimumab was started. Since belimumab was initiated, the patient showed slow but evident improvement (negativization of anti-dsDNA levels, normalization of complement levels, significant X-ray and clinical improvement), allowing to reduce prednisone to 5 mg daily and stop mycophenolate mophetil treatment within six months.

To the best of our knowledge, the case we present is the second pleuritis SLE patient who show positive outcome during belimumab treatment, and the third suffering serositis (pleuritis and/or pericarditis) as well. In our case, a bilateral involvement was seen after intensive immunosuppressant and prednisone therapy. The latter highlights the need to control the underlying disease as, despite receiving intensive immunosuppressant treatment, the patient showed worsening of her pulmonary SLE involvement and evidence of serological SLE flare. Belimumab offered an alternative to better control disease in our case and we suggest including 'serositis' to the spectrum of SLE treatable features with belimumab when other more well-known immunosuppressants fail to control SLE activity.

### Conflict of interest

The authors do not have conflict of interest for this study.

### Bibliografía

- Salman-Monte TC, Carrión-Barberà I, Rodríguez García E. Belimumab, a useful alternative therapy in systemic lupus erythematosus serositis. *Med Clin (Barc).* 2020. S0025-7753(20)30516-9.
- Carrión-Barberà I, Salman-Monte TC, Castell S, Castro-Domínguez F, Ojeda F, Monfort J. Successful treatment of systemic lupus erythematosus pleuropericarditis with belimumab. *Eur J Rheumatol.* 2019;6:150–2.
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271–7.