



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.

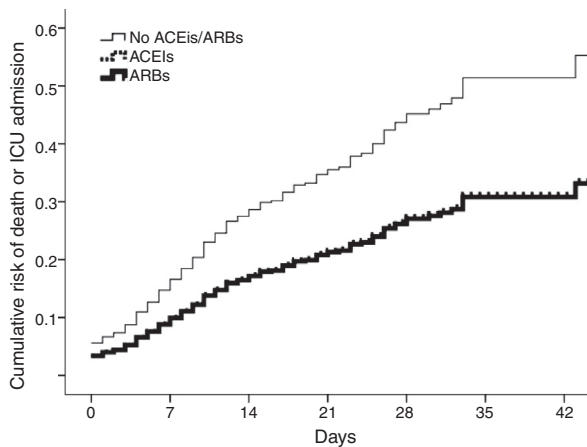


Figure 1. Cumulative risk of death or intensive care unit (ICU) admission in patients on angiotensin-converting enzyme inhibitors (ACEIs) (dotted line), angiotensin receptor blockers (ARBs) (thick line), or neither (thin line). Curves for ACEIs and ARBs overlap, indicating comparably lower risk.

evidence on the benefits and harm of the use of HCQ or chloroquine to treat COVID-19 is still weak and conflicting.^{3,6}

Our patients were older and had a higher burden of cardiovascular risk factors and comorbidities than previous series, all factors that may have contributed to high event rates. Intriguingly, during HCQ coadministration, ACEIs/ARBs were associated with lower hazards of mortality and the need for invasive ventilation, reinforcing previous findings of their lack of detriment in COVID-19.⁵

In a setting similar to ours, Geleris et al.⁶ found no association of HCQ treatment with a higher or lower risk of intubation or death. However, the study did not report the effects of ACEIs/ARBs, which were prescribed in rates similar to those of our cohort.

Our data do not allow confirmation of a possible synergy of ACEIs/ARBs and HCQ or a protective impact of ACEIs/ARBs on the potential cardiac adverse events of HCQ. In many cardiovascular diseases, ACEIs/ARBs exert beneficial effects on cardiac function and endothelial cell dysfunction, which might improve prognosis despite the use of cardiotoxic drugs.

The positive impact of ACEIs and ARBs in our aging patients with cardiovascular morbidities hospitalized for COVID-19, even during treatment with a potentially cardiotoxic agent, has

particular relevance for cardiology practice and strengthens the recommendation to continue treatment with ACEIs/ARBs when indicated.

Acknowledgments

The authors gratefully acknowledge the contribution of Gaia Basini, MEng, to the data collection.

Giuseppe Di Tano,^a Renata De Maria,^{b,*} Marco Loffi,^a Luigi Moschini,^a Gianluca Galeazzi,^a and Gian Battista Danzi^a

^aCardiology Department, ASST Cremona Hospital, Cremona, Italy

^bNational Research Council, Institute of Clinical Physiology, ASST Great Metropolitan Hospital Niguarda, Milan, Italy

* Corresponding author:

E-mail addresses: renata_de_maria@hotmail.com, renata.demaria@ospedaleniguarda.it (R. De Maria).

Available online 9 July 2020

REFERENCES

- McKee DL, Sternberg A, Stange U, Laufer S, Naujokat CP. Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacol Res.* 2020;157:104859.
- Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, Michael White C. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: a living systematic review. *Ann Intern Med.* 2020. <http://dx.doi.org/10.7326/M20-2496>.
- Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med.* 2020;46:586–590.
- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020;17:259–260.
- Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino Sr RB, Harrington DP. Inhibitors of the renin-angiotensin-aldosterone system and Covid-19. *N Engl J Med.* 2020;382:2462–2464.
- Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020;382:2411–2418.

<https://doi.org/10.1016/j.rec.2020.07.001>
1885-5857/

© 2020 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

D-dimer and right ventricular abnormalities as prognostic factors in critically ill COVID-19 patients



Dímero D y alteraciones del ventrículo derecho como factores pronósticos en pacientes críticos con COVID-19

To the Editor,

Coronavirus disease 2019 (COVID-19) seems to be associated with a higher risk of myocardial injury, especially in critically ill patients.¹ Previous definitions of acute COVID-19 cardiovascular syndrome² have been heterogeneous, and therefore its true incidence, clinical relevance and prognostic impact remain unclear. The aim of this study was to analyze echocardiographic abnormalities and biomarkers in COVID-19 patients requiring intensive care and their association with 30-day survival.

Observational, prospective cohort study of patients admitted to the intensive care unit (ICU) of *Hospital Universitario La Paz* (Madrid, Spain) with confirmed COVID-19 infection and acute respiratory distress syndrome between March 1 and April 8, 2020. We analyzed serum biomarkers in all patients. Following current recommendations,^{3,4} a focused cardiac ultrasound study³ was performed by accredited cardiologists. The main outcome was 30-day survival. Major cardiovascular events during follow-up were recorded, including myocarditis, pericarditis, pulmonary embolism (PE), and ventricular arrhythmias. The patients were followed up until hospital discharge or death. The study was conducted in compliance with the Declaration of Helsinki and was approved by the ethics committee of our institution.

Fifty-two patients were included (table 1), and the median follow-up was 46 [22–54] days. The most common findings in our study were right ventricular (RV) abnormalities, mainly RV systolic

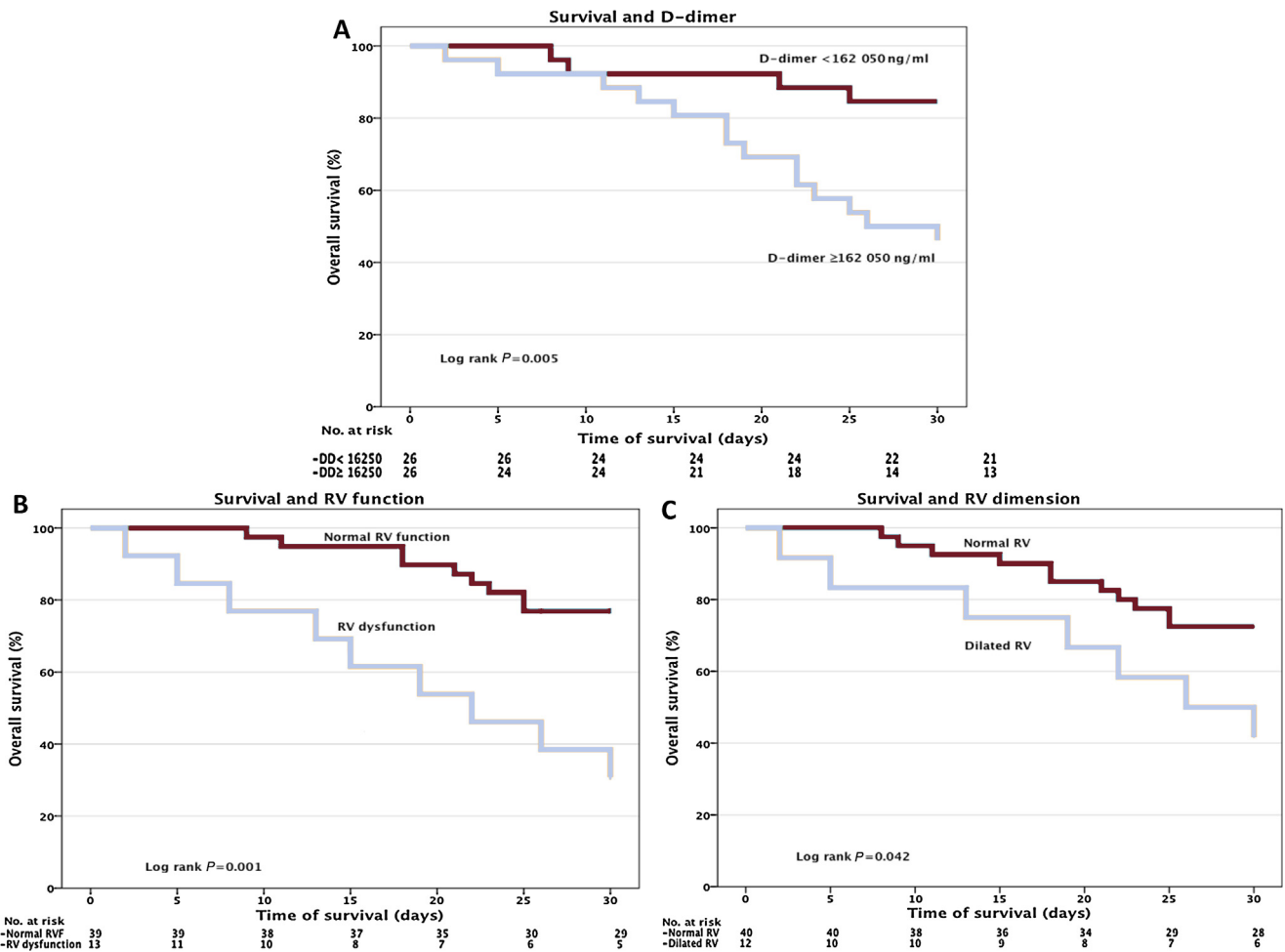


Figure 1. Survival analyses. Kaplan-Meier survival curves representing cumulative survival at 30 days by A: peak D-dimer values (considering a median value of 16 250 ng/mL); B: right ventricular function; and C: right ventricular dimension. RV, right ventricular; RVF, right ventricular function; DD, D-dimer; No., number.

dysfunction (26.9%) and dilatation (25.0%). Left ventricular systolic dysfunction and dilatation were less prevalent in our cohort.

Median [interquartile range] high-sensitivity troponin I (hs-TnI) and peak D-dimer values are shown in table 1. D-dimer was significantly higher in patients with RV systolic dilatation (69 645 [36 621-122 040] vs 11344 [6519-52 363] ng/mL; $P = .02$) and dysfunction (63 872 [25 284-112 085] vs 10 972 [6498-59 450] ng/mL; $P = .01$) compared with those with a normal RV. In contrast, median hs-TnI was not associated with a higher incidence of cardiac structural abnormalities. No differences were found between positive end-expiratory pressure and RV function or dimension.

Kaplan-Meier survival analyses were performed for all patients. Survival at 30 days was significantly lower in patients with higher D-dimer values than the median (figure 1). Lower 30-day survival rates were also found in patients with RV dysfunction and dilatation.

A multivariate Cox-proportional hazards regression analysis was performed including age, D-dimer values, and RV dysfunction. RV function was identified as an independent predictor of 30-day survival in our cohort (hazard ratio, 3.71; 95% confidence interval, 1.28-10.76; $P = .02$).

The major cardiovascular events rate was relatively low in our cohort. PE occurred in 3 patients, who required reperfusion

therapy; only 1 was confirmed by catheter pulmonary angiography, showing multiple thrombi in the distal vessels. Findings compatible with pericarditis were present in 2 patients and 3 showed data consistent with myocarditis. No ventricular arrhythmias were identified in our cohort.

RV dysfunction and dilatation are common echocardiographic findings in ICU patients and are associated with worse outcomes. In addition, higher D-dimer levels suggest a prothrombotic state and correlate with RV abnormalities and worse survival. An isolated rise in hs-TnI does not seem to be associated with structural or clinically relevant cardiac abnormalities in COVID-19 patients.

These findings may be related to an increased prevalence of PE in COVID-19 patients. Nevertheless, in the ICU scenario, patients with acute respiratory distress syndrome requiring mechanical ventilation may also develop acute cor pulmonale, which may be indistinguishable. Surprisingly, the high positive end-expiratory pressure levels shown in our population did not correlate with RV abnormalities. Therefore, a hypothesis of a pulmonary prothrombotic state impacting on the RV should be raised and might be related to worse outcomes. Our data are consistent with autopsy reports⁵ and computed tomography scans⁶ of COVID-19 patients, showing RV dilatation and multiple thrombi in small pulmonary vessels.

Table 1

Patient characteristics

n = 52	
Variable	
Age, y	59.3 (13.5)
Male sex	36 (69.2)
Hypertension	21 (40.4)
Diabetes	15 (28.8)
Dyslipidemia	17 (32.7)
Ischemic heart disease	1 (1.9)
Atrial fibrillation	2 (3.8)
Chronic pulmonary disease	4 (7.7)
Cerebrovascular disease	0 (0)
Chronic kidney disease	1 (1.9)
Mechanical ventilation	46 (88.5)
Positive end-expiratory pressure, mmHg	12.2 (2.9)
Time since symptom onset at admission, d	10 [7–12]
Time since symptom onset at echocardiography, d	16 [12–22]
Time of ICU admission at echocardiography, d	6 [2–10]
Elevated hs-TnI	31 (59.6)
Peak hs-TnI, ng/L	59.3 [29.2–327.8]
Peak D-dimer, ng/mL	16 250 [6673–72 620]
LVEF	57.2 (8.2)
Left ventricular dysfunction (LVEF < 50%)	9 (17.3)
LVEF 41%–50%	4 (7.7)
LVEF 31%–40%	5 (9.6)
LVEF < 30%	0 (0)
Left ventricular hypertrophy	16 (30.8)
Mild	8 (15.4)
Moderate	8 (15.4)
Left ventricular dilatation	9 (17.3)
Mild	4 (7.7)
Moderate	5 (9.6)
Right ventricular dysfunction	14 (26.9)
Mild	6 (11.5)
Moderate	6 (11.5)
Severe	2 (3.8)
Right ventricular dilatation	13 (25.0)
Mild	9 (17.3)
Moderate	3 (5.8)
Severe	1 (1.9)
Valvular disease	16 (30.8)
Tricuspid regurgitation	13 (25.0)
Mild	8 (15.4)
Moderate	4 (7.7)
Severe	1 (1.9)
Aortic stenosis	3 (5.8)
Estimated pulmonary artery systolic pressure, mmHg	38.9 (8.2)
Inferior vena cava dimension, mm	18.4 (3.9)
Inferior vena cava respiratory variations	8 (15.4)
Outcomes at time of analysis	
Discharged from ICU	9 (17.3)
Death	5 (9.6)

ICU, intensive care unit; hs-TnI, high-sensitivity troponin I; LVEF, left ventricular ejection fraction.

Data are expressed as No. (%), mean \pm standard deviation, or median [interquartile range].

Because our study is a single-center experience with a small sample size, it has some limitations. The main limitation is that we did not perform computed tomography due to the patients' critical status and isolation protocols. Further research is needed to confirm our findings.

Acknowledgements

We thank Drs. M.J. Asensio Martín, J.M. Añón Elizalde, S.M. Sánchez Sánchez, and A. García de Lorenzo for their contribution to this article.

Oscar Gonzalez-Fernandez,^{a,◇,*} Ines Ponz de Antonio,^{a,◇} Sandra O. Rosillo Rodriguez,^{a,◇} Jose Ruiz Cantador,^a Juan C. Figueira Iglesias,^b and Jose L. Lopez-Sendon Hentschel^{a,c}

^aDepartamento de Cardiología, Hospital Universitario La Paz, Madrid, Spain

^bDepartamento de Cuidados Intensivos, Hospital Universitario La Paz, Madrid, Spain

^cInstituto de Investigación Hospital Universitario La Paz (IdiPaz), Madrid, Spain

* Corresponding author:

E-mail address: ojog_1@hotmail.com (O. Gonzalez-Fernandez).

◇ These authors contributed equally to this article as coauthors.

Available online 16 July 2020

REFERENCES

- Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan. *China JAMA*. 2020;323:1061–1069.
- Hendren NS, Drazner MH, Bozkurt B, Cooper LT. Description and propose management of Acute COVID-19 Cardiovascular Syndrome. *Circulation*. 2020. <http://dx.doi.org/10.1161/CIRCULATIONAHA.120.047349>.
- Skulstad H, Cosyns B, Popescu BA, et al. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. *Eur Heart J Cardiovasc Imaging*. 2020. <http://dx.doi.org/10.1093/ehjci/jeaa072>.
- Kirkpatrick J, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE Statement on Protection of Patients and Echocardiography Service Providers During the 2019 Novel Coronavirus Outbreak. *J Am Coll Cardiol*. 2020. S0735-1097(20)34815-4.
- Fox SE, Atmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. *MedRxiv*. 2020. <http://dx.doi.org/10.1101/2020.04.06.20050575>.
- Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020. S0049-3848(20)30120-1.

<https://doi.org/10.1016/j.rec.2020.07.004>
1885-5857/

© 2020 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.