

RACCOVID-19: First Argentine Registry of Cardiovascular Complications in Patients with COVID-19

RACCOVID-19: primer Registro Argentino de Complicaciones Cardiovasculares en pacientes con COVID-19

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ABSTRACT

Background: Coronavirus disease (COVID-19) has caused one of the largest pandemics known to date. The Argentine Society of Cardiology (SAC) and the Argentine Federation of Cardiology (FAC) have developed the First Argentine Registry of Cardiovascular Complications in COVID-19 patients (RACCOVID-19) with the aim of performing a nationwide review of their impact in the in-hospital evolution of these patients.

Objectives: The aim of this study was to record cardiovascular complications in hospitalized patients for COVID-19, and to evaluate risk predictors of these complications and their prognostic impact.

Methods: A total of 2750 patients from 50 centers in 11 provinces of the country were included from May 18 to October 31, 2020.

Results: Mean age was 57 ± 18 years, with 60.2% prevalence of male gender. Cardiovascular complications occurred in 15.3% of cases. Heart failure (43.5%), arrhythmias (33.5%) and myocardial injury (31.1%) were the most relevant complications. Mortality was 19.3%, and a predictive model of in-hospital survival included age, male gender, admission hematocrit and creatinine, history of previous diseases, severe forms of COVID-19 presentation and cardiovascular complications.

Conclusions: The RACCOVID-19 registry showed 15.3% of cardiovascular complications. Overall mortality was 19.3%, and cardiovascular complications together with other presentation variables and the clinical severity of COVID-19 are part of a clinical risk profile associated with higher mortality.

Key words: Coronavirus disease 19 (COVID-19) - Cardiac complications - Mortality- Registries – Argentina

RESUMEN

Introducción: La enfermedad por coronavirus (COVID-19) ha causado una de las mayores pandemias conocidas al día de la fecha. La Sociedad Argentina de Cardiología (SAC) y la Federación Argentina de Cardiología (FAC) elaboraron el primer Registro Argentino de Complicaciones Cardiovasculares en pacientes con COVID-19 (RACCOVID-19), con el propósito de relevar, a nivel nacional, su impacto en la evolución hospitalaria de estos pacientes.

Objetivos: Documentar la aparición de complicaciones cardiovasculares en pacientes internados por COVID-19 y evaluar predictores de riesgo de dichas complicaciones y su impacto pronóstico.

Material y Métodos: Se incluyeron datos de 2750 pacientes en 50 centros de 11 provincias del país, desde el 18 de mayo hasta el 31 de octubre de 2020.

Resultados: La edad promedio fue de 57 ± 18 años y hubo predominio de sexo masculino (60,2%). La tasa de complicaciones cardiovasculares fue del 15,3%. La insuficiencia cardíaca (43,5%), las arritmias (33,5%) y el daño miocárdico (31,1%) fueron las complicaciones más frecuentes. La mortalidad fue del 19,3%. Un modelo de predicción de sobrevida en la etapa hospitalaria incluyó las siguientes variables: edad, sexo masculino, valores de hematocrito y creatinina al ingreso, existencia de antecedentes patológicos, formas de presentación de COVID-19 graves y presencia de complicaciones cardiovasculares.

Conclusiones: El registro RACCOVID-19 mostró una tasa de complicaciones cardiovasculares del 15,3%. La mortalidad total del registro fue del 19,3% y las complicaciones cardiovasculares junto con otras variables de presentación, así como la gravedad del cuadro clínico de COVID-19, forman parte de un perfil de riesgo clínico asociado a mayor mortalidad.

Palabras clave: COVID-19 -Complicaciones cardiovasculares - Mortalidad - Registros - Argentina.

Abbreviations

ACE2	Angiotensin-converting enzyme 2	ICU	Intensive care unit
COPD	Chronic obstructive pulmonary disease	IQR	Interquartile range
COVID-19	Coronavirus disease 19	SAC	Argentine Society of Cardiology
FAC	Argentine Federation of Cardiology	SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
HIV	Human immunodeficiency virus.		

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INTRODUCTION

Coronavirus disease (COVID-19) has caused one of the largest known pandemics to date. Although it started in China in December 2019, by March 2020, the number of cases outside that country was experiencing an exponential growth that far exceeded that of the Asian country, which is why the World Health Organization (WHO) declared it a pandemic. At that time the first case appeared in Argentina. From the beginning, the interaction of this infection with the cardiovascular system was known at multiple levels, causing increased morbidity in patients with underlying pathologies and the development of myocardial damage and ventricular dysfunction. (1,2)

COVID-19 is caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). This is a new single-stranded RNA virus, the seventh known human coronavirus. Probably, and like the other coronaviruses, this one originated in bats, since it shares 89-96% of nucleotides with other coronaviruses coming from that animal. (3)

SARS-CoV-2 infection is caused by the binding of viral surface proteins to the human angiotensin-converting enzyme 2 (ACE2) receptor, with subsequent activation with transmembrane proteases. (4, 5) ACE2 is expressed in the lung, where the main entrance to the body is observed. Concomitantly, this enzyme is found in high concentrations in the heart, where it counteracts the effect of angiotensin II in conditions of excessive activation of the renin-angiotensin system, as occurs in the population with hypertension or heart failure. (6, 7)

Multiple COVID-19 case reports suggest that patients with underlying pathologies are at greater risk of complications or mortality, with higher incidence of myocardial injury (defined by increased ultrasensitive troponin concentration), shock, and arrhythmias. (8, 9)

Faced with this critical and threatening reality, and observing the interindividual variations according to the countries, we are compelled to know the prognosis and cardiovascular complications in our population.

The scientific societies of cardiology in Argentina, the Argentine Society of Cardiology (SAC) and the Argentine Federation of Cardiology (FAC), have vast experience in registries and educational programs to improve cardiovascular care. That is why both societies have developed the first Argentine Registry of Cardiovascular Complications in patients with COVID-19 (RACCOVID-19), with the aim of recording the development of cardiovascular complications in patients with COVID-19 admitted to different health centers in our country, and evaluating risk predictors of cardiovascular complications, their prognostic impact and hospital evolution.

METHODS

A nationwide, prospective, observational, multicenter registry was carried out, including patients above 18 years of age who arrived to the participating centers with a confirmed

diagnosis of COVID-19 that required admission or hospitalization in any area of the institution. The exclusion criterion was the presence of ongoing decompensated cardiovascular disease initiated up to 15 days before the confirmation of the COVID-19 diagnosis.

Any of the following conditions was considered a cardiovascular complication:

- Acute myocardial injury (at least two increased or decreased high-sensitivity cardiac troponin assessments, with at least one value above the reference 99th percentile).
- Decompensated heart failure, evaluated by two cardiologists or intensive care specialists.
- New supraventricular or ventricular cardiac arrhythmia.
- Cardiogenic shock.
- New myocardial motility disorders by transthoracic echocardiography (in at least three segments).
- Drop in left ventricular ejection fraction greater than 10% with respect to the baseline echocardiogram.
- Signs of diastolic dysfunction by transthoracic echocardiogram (at least two of the following: E/e' ratio greater than 14, pseudonormal or restrictive filling pattern, pulmonary systolic blood pressure >50 mm Hg, inferior vena cava <21 mm, with collapse <50%).
- Signs of venocapillary congestion by pulmonary ultrasound (greater than 4 pulmonary comet-tail images/Kerley B lines by pulmonary ultrasound in at least 2 segments).
- New acute myocardial infarction (ischemic symptoms, changes in the electrocardiogram ST-T segment or development of pathological Q waves, imaging evidence of a myocardial wall motion disorder, or identification of coronary thrombus).
- New evidence of deep vein thrombosis or pulmonary embolism by any method.
- Myocarditis, diagnosed by clinical suspicion, myocardial biopsy, cardiac magnetic resonance or another method.

Procedure

Different centers in the country were invited to participate in the registry. The patients were entered into the registry by the investigating cardiologist of each institution. Patient identification included center number, followed by the patient's order number from each registered and licensed center.

Registration was anonymous to preserve the privacy and confidentiality of personal data. There was no follow-up due to the particular development of the pandemic, so the registration procedure was modified in order not to require informed consent from each patient (Amendment number 1 of July 10, 2020). Patients were registered from May 18 to October 31, 2020 (Amendment number 2 of September 18, 2020).

Nationality, anthropometric data, medical coverage, cardiovascular risk factors, and pathological and cardiac history were recorded, as well as whether patients were receiving immunosuppressive treatment for any disease. Regarding hospitalization for COVID-19, data on the reason for consultation and lab tests on admission were collected together with the most important pathological value of each variable and the value prior to discharge or death. Laboratory data related to the infection and cardiovascular complications, such as D-dimer and troponin, were requested. In addition, admission to critical care units and cardiovascular complications, including myocardial injury, acute myocardial infar-

tion, heart failure, cardiogenic or mixed shock, arrhythmias, QT prolongation, and thromboembolic disease were recorded. Moreover, the type of treatment received, general and specific against COVID-19, was recorded. All data was uploaded using the REDcap platform.

Statistical analysis

Due to the fact that the registry of an emerging pathology was developed, a formal sample size calculation was not carried out. Continuous data are expressed as mean or standard deviation if the distribution is normal, or median and interquartile range (IQR) 25-75 in the case of non-normal distribution. The assumption of normality was evaluated with the Shapiro-Wilk test with Q-Q (quantile-quantile) plot. Categorical data are presented as numbers and percentages. To assess the association between quantitative variables, Student's t test or the Mann-Whitney U test was used in case of normal and non-normal distribution, respectively. To describe the association between continuous variables in more than two groups, ANOVA or its non-parametric equivalent, the Kruskal-Wallis test, was used according to data distribution. Qualitative variables were analyzed with the chi-square test. Multivariate regression models were used to evaluate evolution predictors, which according to the dependent variables to be analyzed, could include linear, logistic, Cox proportional hazard or Poisson regression, and if they were continuous, dichotomous variables, time to the event or counts, respectively. A nominal value of $p < 0.05$ was considered statistically significant.

Ethical considerations

The protocol was evaluated and approved by the SAC Bioethics Committee. The ethics committee approval and the medical director authorization of each participating center were requested. The protocol was registered in the PRIISA system under number 1394.

RESULTS

A total of 379 patients were included; mean age was Fifty centers from 11 provinces of the country participated in the RACCOVID-19 registry. In 53.8% of cases, patients were admitted to establishments in the Autonomous City of Buenos Aires, 26.9% to centers in the province of Buenos Aires and 29.3% to centers distributed in the rest of the provinces. (Table 1)

The total number of patients admitted to the registry was 2750, with mean age of 57 ± 18 years and 60.2% men. Among these patients, 88.8% were of Argentine nationality and 73.3% had some medical coverage or prepaid system. The clinical characteristics of the registered population, including cardiovascular risk factors and pathological and cardiovascular history, are shown in Table 2.

Of the registered patients, 54.1% were receiving cardiological medication before admission. The most frequent medications were angiotensin converting enzyme inhibitors (ACEI) (19.9%), statins (16.2%), beta blockers (16.1%), aspirin (12.2%) and angiotensin II receptor blockers (ARBs) (12%). (Table 3)

Data obtained from the lab tests on admission were (median and IQR 25-75): hematocrit 40% (36-43); leukocytes 6885/mm³ (5200-9900); platelets 196 000/mm³ (150 000-249 250); urea 34 mg/dL (25-48), creatinine 0.9 mg/dL (0.72-1.12) and total bilirubin 0.5 mg/dL (0.39-0.75). The higher values obtained were erythrocyte sedimentation rate, 55 mm/h (33-80); ferritin 800 ng/mL (293-1603); lactate dehydrogenase 498 U/L (309-705) and D-dimer 417 ng/mL (1.92-1018).

The clinical status of COVID-19 patients had the following distribution: asymptomatic/mild, 1308 (50.7%); moderate/severe 941 (36.5%) and critical 330 (12.8%). Hospital stay was 10 days (IQR 25-75: 6-16). A total of 410 patients (14.9%) required mechanical ventilation, 13.4% of the patients received inotropic agents and only 0.6% received extracorporeal membrane oxygenation (ECMO) or another type of circulatory support. The length of stay in the intensive care unit was 8 days (IQR 25-75: 4-15).

The most common symptoms were fever (65.9%); cough (49.6%); dyspnea (41.4%); myalgia (26.5%); odynophagia (18.2%) and anosmia (10.4%). Specific treatment against COVID-19 was administered to 1129 patients (41.1%); including corticosteroids (87.6%), hydroxychloroquine alone or in combination with azithromycin (5.2%), antiviral agents: lopinavir/ritonavir/remdesivir (3.5%), interferon B (0.3%), col-

Table 1. RACCOVID-19: Distribution of admitted cases

Province	N.° of centers	N.° of patients	Percentage
CABA	15	1480	53.8
Buenos Aires	17	739	26.9
Córdoba	4	300	10.9
Mendoza	2	88	3.2
Santa Fe	5	76	2.7
Chaco	2	53	1.9
Salta	1	5	0.2
Corrientes	1	3	0.1
Entre Ríos	1	3	0.1
Formosa	1	2	0.1
Neuquén	1	1	0.0
Total	50	2750	100

CABA: Autonomous City of Buenos aires

Table 2. RACCOVID-19: Baseline characteristics of the included population

Variable	Frequency	Percentage
Age (mean ± SD), years (n=2530)	57± 18	
Male gender (n=2530)	1541	60.2
CV risk factors (n=2597)	1750	67.4
-Hypertension	1133	43.6
-Diabetes mellitus	480	18.4
-Dyslipidemia	399	15.3
-Obesity	799	30.7
-Smoking	399	15.3
Pathological history (n=2580)	1072	41.6
-COPD/asthma	248	9.6
-Chronic kidney failure/dialysis	139	5.3
-Oncohematological diseases	120	4.6
-Immunosuppressive treatment	118	4.6
-HIV	44	1.7
-Tuberculosis	31	1.2
-Chagas disease	30	1.2
-Collagenopathy	32	1.2
Cardiovascular history (n=2750)	1218	44.2
Hypertension	1133	43.9
Ischemic heart disease	210	7.6
Arrhythmias	219	8.0
Heart failure	174	6.3
Valvular disease	81	2.9
PH	31	1.1
Congenital heart disease	13	0.5

SD: Standard deviation, CV: Cardiovascular. COPD: Chronic obstructive pulmonary disease. HIV: Human immunodeficiency virus, PH: Pulmonary hypertension

chicine (0.2%) and others, including plasma (47.3%). Anticoagulation was indicated in 589 patients (21.4%).

Cardiovascular complications

The rate of cardiovascular complication was 15.3% (420 patients). The average age of this group was 67±14 years, with prevalence of male gender (68%). In 88.3% cases patients had some coronary risk factor, 80.4% had cardiovascular disease history, and only 26.4% had another pathological antecedent. Heart failure was the most common complication, present in 183 patients (43.5%), and included the clinical definition determined by two different cardiologists or intensive care specialists, cardiogenic shock, diastolic abnormalities by Doppler echocardiography, and pulmonary congestion by echopleura. Arrhythmias were the second most frequent complication, found in 141 patients (33.5%), encompassing atrial fibrillation, other supraventricular arrhythmias, ventricular

Table 3. RACCOVID-19: previous cardiology medication

	Frequency	Percentage
Previous medication	1481	53.8
ACEI	544	19.7
Statins	443	16.1
Beta-blockers	448	16.2
ASA	334	12.1
ARBs	327	11.8
Calcium Blockers	136	4.9
Oral anticoagulation	122	4.4
Antidosterone agents	71	2.5
Amiodarone	41	1.4
NSAID	28	1.0
Digoxin	19	0.7
Sacubitril/valsartan	5	0.1

ACEI: angiotensin converting enzyme inhibitors. ASA: acetylsalicylic acid. ARBs: angiotensin II receptor blockers. NSAID: non-steroidal anti-inflammatory drugs.

arrhythmias, and QT interval prolongation. Atrial fibrillation was the most common arrhythmia reported in 74 patients (17.6% of all complications). Myocardial damage occurred in 131 patients (31.1%), comprising myocardial injury, acute myocardial infarction, and motility disorders on echocardiography. Thromboembolic complications were observed in 47 patients (11.1%), involving pulmonary thromboembolism, deep vein thrombosis, and arterial embolisms. Myocarditis was reported in 1.9% of patients. (Figure 1)

During hospitalization, 53 patients suffered from acute myocardial infarction; ST-segment elevation acute myocardial infarction occurred in 24 patients and 22 of them (91.7%) received some reperfusion strategy, with primary percutaneous coronary intervention (PCI) in 66.7% and thrombolytic agents in 25%.

Mortality. Univariate and multivariate analysis

Hospital discharge rate was 80.6%: 2102 patients (77.7%) were discharged and 79 (2.9%) were transferred to another institution, while 523 (19.3%) died during hospitalization. Mortality included 201 patients with cardiovascular complications (47.86%). The average age of deceased patients was 69.8 years and of that of discharged or transferred patients 54.3 years (p < 0.0001).

A death prediction model consisting of seven variables with high discrimination capacity (area under the ROC curve 0.9255) and calibration (Hosmer-Lemeshow test, p = 0.11) to predict in-hospital mortality was built with a series of variables significantly related to mortality and other variables considered clinically relevant, including age, male gender, medical history, hematocrit and creatinine on admission, more severe forms of COVID-19, and cardiovascular complications (myocardial injury, heart failure, arrhythmias, thromboembolism, and myocarditis) (Table 4).

DISCUSSION

To date, this is one of the largest registries in a country concerned with cardiovascular complications in COVID-19 patients. It is important to clarify that, during the recorded period, all those affected by COVID-19 were hospitalized for clinical control in our country. The prevalence of patients admitted to the registry hospitalized in centers of the Autonomous City of Buenos Aires and the Province of Buenos Aires agrees with the time-lag in the rate of infections that occurred between these districts and the rest of the country. (10)

The average age of 57 years and the predominance of male patients (60.2%) were consistent with those of other registries in 2020. The most frequent comorbidities were hypertension, obesity and diabetes, in agreement with data emerging from other registries. (11) We must recall that the last National Risk Factor Survey showed these three factors as the most frequent comorbidities. (12)

The incidence of cardiovascular complications was 15.3%, the most common being heart failure, myocardial injury, confirmed by increased blood troponin levels, and atrial fibrillation. Patients with pre-existing diseases or cardiovascular risk factors are more likely to have complications; also, they present with more severe systemic inflammation and higher levels of inflammatory markers. (13) It is important to highlight that, in our registry, these patients were older, with more risk factors and history of cardiovascular disease.

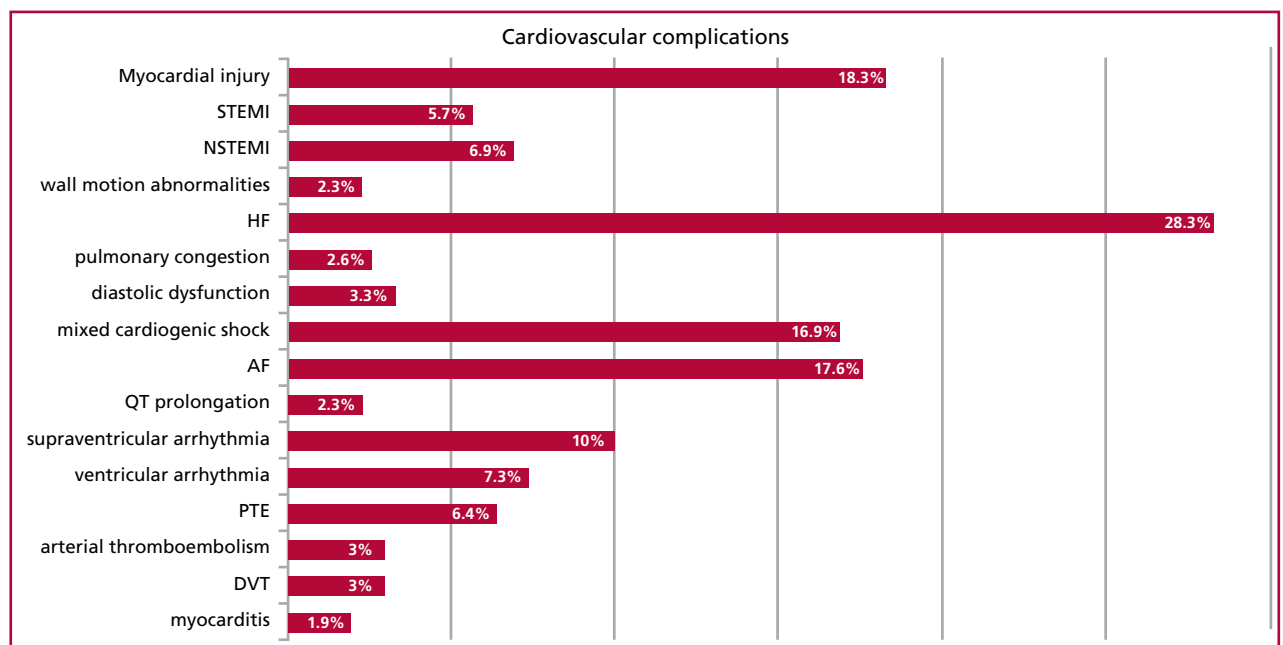
Heart failure was the most frequent complication. The systemic inflammatory response syndrome due

to viral infection could be the cause for the development of heart failure or the exacerbation of the pre-existing condition. (14) This complication is clearly a factor with worse prognosis. (15) An increased risk of in-hospital death was observed in patients who suffered from heart failure during hospitalization for COVID-19. (16)

Among the arrhythmic complications, atrial fibrillation was the most frequent. COVID-19, like all infections, can trigger fever-induced atrial fibrillation, hypoxia, and adrenergic tone. Its incidence during hospitalization in patients with severe pneumonia and sepsis is high, and treatment should consider ventricular rate control, rhythm control, and thromboembolic prophylaxis.

Regarding myocardial injury, there are several non-invasive diagnostic methods available to identify the type of injury, such as enzyme markers, echocardiography, and cardiac magnetic resonance imaging. According to different reports, acute myocardial infarction can occur in 7-17% of patients hospitalized for COVID-19 and in 22-31% of those admitted to an intensive care unit (ICU). (13,17) In our registry, 91.7% of patients with STEMI received some reperfusion strategy, and, for the most part, it was with primary PCI, which was carried out in compliance with the protocols required for the protection of healthcare personnel.

There was a low rate of myocarditis and thromboembolic complications, although the reported incidence of thrombotic complications in patients admitted to the ICU is high. This discrepancy is probably due to the fact that, in our registry, half of hospitalized



STEMI: ST segment elevation acute myocardial infarction, NSTEMI: non-ST segment elevation acute myocardial infarction, HF: Heart failure, AF: Atrial fibrillation, PTE: Pulmonary thromboembolism, DVT: Deep vein thrombosis

Fig. 1. RACCOVID-19: types and frequencies of cardiovascular complications

Table 3. RACCOVID-19: previous cardiology medication

Variable	OR (95% CI)	p
Age	1.07 (1.05–1.08)	<0.0001
Male gender	1.51 (1.05–2.16)	<0.0001
Creatinine on admission	1.23 (1.09–1.37)	<0.0001
Hematocrit on admission	0.94 (0.92–0.97)	<0.0001
Pathological history	1.60 (1.14–2.72)	0.006
CV complications	1.55 (1.08–2.22)	0.017
Severe clinical condition *	6.37 (4.09–9.93)	<0.0001

CV: Cardiovascular

* It includes: moderate/severe and critical condition

patients presented asymptomatic or mild COVID-19.

Both the rate of cardiovascular complications and overall mortality in our registry were similar to those reported in other international registries and, above all, to those arising from the multicenter CAPACITY-COVID registry, which covered 13 countries and was designed to evaluate cardiovascular complications. This registry reported 11.6% of cardiovascular complication and 19.8% of overall mortality, similar to those of our registry. (18, 19)

The RACCOVID-19 registry allowed the identification of a series of clinical variables such as age, gender, pathological history, more severe forms of the disease, and hematocrit and creatinine values on hospital admission, which were associated with the development of cardiovascular complications and strongly related with the patients' prognosis.

Limitations

Although RACCOVID-19 is the only national registry focused on the evolution of COVID-19 and cardiovascular complications, its representativeness is limited. Most of the centers were selected for their relationship with the organizing scientific societies. An online database was used for uploading, with suboptimal data monitoring. Finally, the data collection period was short and took place during the first wave of the disease in our country.

CONCLUSIONS

The RACCOVID-19 registry showed 15.3% of cardiovascular complications in patients hospitalized for COVID-19. Overall mortality was 19.3%, and cardiovascular complications together with other presentation variables as well as the clinical severity of COVID-19 are part of a clinical risk profile associated with higher mortality.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

REFERENCES

- Dong E, Du H and Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;533-4. [https://doi.org/10.1016/S1473-3099\(20\)30120-1](https://doi.org/10.1016/S1473-3099(20)30120-1).
- Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. <https://doi.org/10.1161/CIRCULATIONAHA.120.046941>
- Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med* 26:450-2. <https://doi.org/10.1038/s41591-020-0820-9>.
- Zhang T WQ, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. *Curr Biol* 2020;30:1346-51. <https://doi.org/10.1016/j.cub.2020.03.022>.
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, SchiergensTS, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181:271-80.e8 <https://doi.org/10.1016/j.cell.2020.02.052>.
- Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y and Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *bioRxiv* 2020. <https://doi.org/10.1101/2020.01.26.919985>.
- Tikellis C and Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *Int J Pept* 2012;2012:256294. <https://doi.org/10.1155/2012/256294>
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; <https://doi.org/10.1001/jama.2020.1585>
- <https://www.argentina.gov.ar/salud/coronavirus/informacion-epidemiologica>
- Núñez-Gil IJ, Fernández-Pérez C, Estrada V, Becerra-Muñoz VM, El-Batrawy I, Uribarri A, et al. Mortality risk assessment in Spain and Italy, insights of the HOPE COVID-19 Registry Intern Emerg Med 2021;16:957-66. <https://doi.org/10.1007/s11739-020-02543-5>
- 4ª Encuesta nacional de factores de riesgo 2018. Ministerio de salud de la Nación. https://bancos.salud.gob.ar/sites/default/files/2020-01/4ta-encuesta-nacional-factores-riesgo_2019_principales-resultados.pdf
- Babapoor-Farrikhran S, Gill D, Walker J, Tarigathi Rasekhi R, Bozorgnia B, Amanullah A. Cardiovascular disease and COVID-19: possible mechanisms. *Life Sci* 2021;15:477
- Yang C, Jin Z. An Acute Respiratory Infection Runs Into the Most Common Noncommunicable Epidemic-COVID-19 and Cardiovascular Diseases. *JAMA Cardiol* 2020;5:743-4 <https://doi.org/10.1001/jamacardio.2020.0934>.
- Mehra MR, Ruschitzka F. COVID-19 Illness and Heart Failure: A Missing Link? *JACC Heart Fail* 2020;8:512-4. <https://doi.org/10.1016/j.jchf.2020.03.004>.
- Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. *N Engl J Med* 2020;382:102 <https://doi.org/10.1056/NEJMoa2007621>
- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny D. Potential effect of coronaviruses on the cardiovascular system. *JAMA Cardiol*. 2020;5(7):831-840
- Bavishi C, Maddox TM, Messerli FH. Coronavirus disease 2019 (COVID 19) infection and renin angiotensin system blockers. *JAMA Cardiol* 2020;5:745-7
- Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbreras-Bermejo C, Ramos-Rincón JM, Roy-Vallejo E, et al. Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19. *Rev Clin Esp* 2020;220:480-94.
- Linschoten M et al. Cardiac complications in patients hospitalized with COVID-19. The CAPACITY -COVID collaborative consortium. *Eur Heart J Acute Cardiovasc Care* 2020;9:817-23. <https://doi.org/10.1177/2048872620974605>