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REFERENCES

1. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004.
2. Perlman A, Hirsh Raccah B, Matok I, Muszkat M. Cognition and dementia related adverse effects with sacubitril-valsartan: analysis of the FDA Adverse Event Report System Database. 2018. *J Card Fail.* 2018;24:533–536.
3. Patel N, Gluck J. Is Entresto good for the brain? *World J Cardiol.* 2017;9:594.
4. Wooster J, Cook EA, Shipman D. Psychiatric manifestations with sacubitril/valsartan: a case report. *J Pharm Pract.* 2019. http://dx.doi.org/10.1177/0897190019842700.
5. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 5.ª ed. Arlington: American Psychiatric Association; 2013. p. 110-115.

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Association between myocardial injury and prognosis of COVID-19 hospitalized patients, with or without heart disease. CARDIOVID registry

Asociación entre el daño miocárdico y el pronóstico de pacientes hospitalizados por COVID-19, con y sin cardiopatía. Registro CARDIOVID

To the Editor,

In December 2019, a cluster of cases of severe acute respiratory syndromes was first reported in Wuhan (China). A novel coronavirus was isolated and was named SARS-CoV-2.[1] By April 1, 2020, the disease caused by SARS-CoV-2, known as COVID-19 (Coronavirus disease 2019), was declared a global pandemic by the World Health Organization.[2]

Although the main clinical manifestation of this new virus occurs in the respiratory system, other organs such as the heart can also be affected. There are several mechanisms by which SARS-CoV-2 could cause myocardial damage. The presence of angiotensin-converting enzyme-2 receptors (used by this virus to invade the pneumocyte) in cardiomyocytes could be associated with the development of myocarditis, which can cause systolic dysfunction and heart failure (HF).[3] Another mechanism of cardiac damage could be the high degree of inflammatory activity. COVID-19 precipitates a cytokine storm with increased levels of interleukin (mainly 2, 7 and 10) and other proinflammatory cytokines, such as granulocyte-colony stimulating factor and tumor necrosis factor, among other mediators of the systemic and local inflammatory response. This proinflammatory storm can reduce flow to the coronary arteries, as well as destabilize coronary atherosclerosis plaques, associated with a hypercoagulable state that precipitates the microvascular thrombosis responsible for myocardial damage and the consequent elevation of troponin (Tn).[4,5]

In situations of hypoxemia or sustained hypotension, type 2 acute myocardial infarction may also occur. Finally, stress cardiomyopathy or tachycardias due to adrenergic discharge, either endogenous or exogenous, are other forms of myocardial damage related to this virus.[6]

This work was conducted to evaluate the impact on mortality, HF and on both combined of TnI elevation in COVID-19, both in patients with and without previous heart disease (HD), defined as a history of ischemic heart disease, at least moderate heart valve disease, or left ventricular dysfunction (ventricular ejection fraction $< 40\%$).

From March 10 to April 6, 2020, we included all patients with confirmed SARS-CoV-2 infection in our health area who were admitted to hospital (n = 245). Of these, 33 (14.1%) required intensive critical care. A total of 27 deaths were recorded (11%), and 35 (14.3% patients) developed HF. A total of 42 patients (17.1%) had HD. Of these, 15 (35.7%) had elevated Tn compared with 13.3% of patients without HD.

Table 1 summarizes the baseline characteristics of COVID-19 patients and provides a comparison of the cohorts with normal and elevated TnI values, as well as the results of the univariate analysis for the association of death and HF for all hospitalized patients, respectively.

Figure 1A represents the clinical complications observed in patients with high or normal TnI, based on the prior presence of HD. In all groups, TnI elevation identified a group of patients with a worse prognosis, but the rate of events in patients with elevated TnI compared with those with normal TnI was higher in patients without HD than in those with HD.

In the adjusted and nonadjusted analyses of the association between TnI and the clinical complications observed during hospitalization, TnI elevation was associated with higher mortality (odds ratio [OR] 334; 95% confidence interval [95%CI] 4.91-2285.10; $P = .025$), but not with a higher risk of developing HF (OR, 3.12; 95%CI, 0.72-13.63; $P = .130$). The combined outcome of mortality and HF was more frequent (OR, 5.58; 95%CI, 1.24-25-12, $P = .025$) in the group with elevated TnI.

On multivariate analysis of the association between TnI and clinical complications, both in patients with and without previous HD, TnI elevation was related to higher mortality (OR, 4.93; 95%CI, 1.24-19.52; $P = .023$), HF (OR, 4.28; 95%CI, 1.30-14.07; $P = .017$), and with the combined outcome of mortality or HF (OR, 7.09; 95%CI, 2.28-22.03; $P = .001$) in patients without HD, but not in patients with previous HD ($P = .561$, $P = .337$ and $P = .992$, respectively).

Figure 1B describes the relationship between TnI and the predicted probability of death or HF. As Tn rose, there was an increase in the risk of developing adverse outcomes. This relationship was more robust in patients without previous HD.

Tn elevation in patients without HD could indicate more severe infection and respiratory distress, which could determine the prognosis of COVID-19. In contrast, in patients with previous HD, Tn elevation may not only be related to the infectious process, but also to their underlying disease, so that, by itself, it does not identify the severity of COVID-19.

These findings could have relevant clinical implications. Tn elevation allows easy and rapid identification of a group of patients

Table 1
Baseline characteristics of the total and subgroup population and variables associated with mortality and heart failure

Baseline characteristics of the total and subgroup population				
	Total population N = 245 (100%)	Elevated troponin levels n = 42; (17.1%)	Normal troponin levels n = 203 (82.9%)	*P*
Clinical presentation				
Days of symptoms	6.6 ± 4.8	5.4 ± 4.6	6.8 ± 4.8	.077
Fever	198 (80.8)	31 (73.8)	167(82.3)	.205
SaO_2 < 95%	134 (54.7)	30 (71.4)	104 (51.2)	.017
Demographic characteristics				
Age, y	67.6 ± 15.7	77.2 ± 10.8	65.6 ± 15.9	< .001
Female sex	99 (40.4)	12 (28.6)	87 (42.9)	.086
Obesity	27 (11.0)	7 (16.7)	20 (9.9)	.199
Healthworker	12 (4.9)	1 (2.4)	11 (5.4)	.406
Retirement home	8 (3.3)	3 (7.1)	5 (2,5)	.120
Dementia	10 (4.1)	5 (11.9)	5 (2.5)	.005
Dependency	27 (11.0)	12 (28.6)	15 (7.4)	< .001
Cardiovascular risk factors				
Current smoker	7 (2.9)	0 (0.0)	7 (3.4)	.222
Hypertension	117 (47.8)	27 (64.3)	90 (44.3)	.018
Diabetes mellitus	61 (24.9)	20 (47.6)	41 (20.2)	< .001
Dyslipidemia	114 (46.5)	25 (59.5)	89 (43.8)	.064
Peripheral artery disease	20 (8.2)	12 (28.6)	8 (3.9)	< .001
Heart disease				
Isquemic heart disease	24 (9.8)	9 (21.4)	15 (7.4)	.005
Left ventricular disfunction	13 (5.3)	8 (19.0)	5 (2.5)	< .001
Valvular disease	12 (4.9)	2 (4.8)	10 (4.9)	.964
Atrial fibrillation	15 (6.1)	7 (16.7)	8 (3.9)	.002
Pulmonary disease				
Pulmonary disease	48 (19.6)	7 (16.7)	41 (20.2)	.600
COPD/asthma	31 (12.7)	7 (16.7)	24 (11.9)	.390
OSAHS	12 (4.9)	0 (0.0)	12 (5.9)	.106
Other comorbidities				
Renal impairment, eGFR < 30 mL/min	14 (5.7)	9 (21.4)	5 (2.5)	< .001
Stroke/TIA	13 (5.3)	7 (16.7)	6 (3.0)	< .001
Neoplasia	5 (2.0)	4 (9.5)	1 (2.0)	.864
Hypothyroidism	10 (4.1)	2 (4.8)	8 (3.9)	.807
Autoimmune disease	15 (6.1)	2 (4.8)	13 (6.4)	.686
Laboratory test (admitted patients only)				
pO_2 < 60 mmHg	176 (71.7)	36 (85.7)	140 (68.7)	.027
pCO_2 > 45 mmHg	16 (6.3)	7 (16.7)	9 (4.1)	.002
Hemoglobin, g/dL	13.2 ± 1.9	12.3 ± 2.6	13.4 ± 1.7	.015
Leucocytes, $10^3/\mu L$	65 ± 3.4	8.0 ± 4.7	6.2 ± 3.1	.021
Lymphoocytes, $10^2/\mu L$	0.9 ± 0.8	0.7 ± 1.2	0.9 ± 0.7	.099
Platelets, $10^3/\mu L$	201.1 ± 98.3	187.1 ± 108.9	201.9 ± 96.4	.771
Creatinine, mg/dL	1.2 ± 0.9	1.8 ± 1.5	1.0 ± 0.7	.002
D-dimer, ng/mL	2779.8 ± 10370.3	4351.5 ± 6419.8	2460.6 ± 10985.6	.294
Ferritin, ng/mL	926.2 ± 998.4	1291.8 ± 1407.2	856.8 ± 888.6	.090
C-reactive protein, mg/dL	12.2 ± 13.5	15.5 ± 11.7	11.5 ± 13.7	.083
Interleukin-6, pg/mL	113.1 ± 408.0	355.0 ± 942.1	71.3 ± 186.1	.117
Previous treatments				
Antiplatelet therapy	36 (14.7)	14 (33.3)	22 (10.8)	< .001
Anticoagulation	27 (11.0)	12 (28.6)	15 (7.4)	< .001
Beta-blockers	37 (15.1)	14 (33.3)	23 (11.3)	< .001
ACEI/ARB	81 (33.1)	20 (47.6)	61 (30.0)	.028
Corticosteroids	20 (8.2)	4 (9.5)	16 (7.9)	.724

Table 1 *(Continued)*
Baseline characteristics of the total and subgroup population and variables associated with mortality and heart failure

Variables associated with mortality and heart failure						
Variables	Mortality			Heart failure		
	OR	95%CI	*P*	OR	95%CI	*P*
Days of symptoms, per d	0.91	0.83-1.02	.096	1.06	0.99-1.13	.081
Fever	0.81	0.31-2.14	.671	0.77	0.32-1.82	.552
$SaO_2 < 95\%$	4.16	1.52-11.39	.005	4.83	1.93-12.12	.001
Age, per y	1.11	1.06-1.16	< .001	1.02	0.99-1.04	.196
Female sex	0.30	0.11-0.82	.019	0.98	0.47-2.04	.958
Obesity	2.02	0.70-5.88	.195	1.05	0.34-3.24	.934
Health worker	-	-	-	0.53	0.07-4.26	.552
Retirement home	5.32	1.20-23.68	.028	0.85	0.10-7.15	.883
Dementia	3.77	0.91-15.54	.067	-	-	-
Dependency	3.46	1.31-9.19	.013	0.45	0.10-1.98	.291
Current smoker	-	-	-	1.00	0.12-8.57	1.000
Hypertension	1.20	0.54-2.68	.652	1.04	0.51-2.13	.917
Diabetes mellitus	8.14	3.42-19.37	< .001	1.99	0.94-4.25	.073
Dyslipidaemia	1.50	0.67-3.36	.321	1.89	0.91-3.91	.088
Peripheral artery disease	7.23	2.63-19.86	< .001	2.90	1.03-8.14	.044
Ischemic heart disease	4.14	1.53-11.17	.005	2.21	0.81-6.02	.122
Left ventricular dysfunction	5.97	1.80-18.82	.004	4.21	1.29-13.71	.017
Valvular disease	4.57	1.28-16.34	.020	3.53	0.93-11.47	.066
Atrial fibrillation	4.73	1.48-15.08	.009	3.33	1.07-10.42	.038
Pulmonary disease	2.29	0.96-5.49	.062	1.52	0.66-3.50	.327
COPD/asthma	2.21	0.81-5.99	.120	1.94	0.76-4.91	.164
OSAHS	2.90	0.73-11.46	.128	1.21	0.25-5.78	.809
eGFR < 30 mL/min	7.50	2.38-23.68	.001	1.70	0.45-6.41	.436
Stroke/TIA (prior)	4.04	1.15-14.15	.029	0.49	0.06-3.85	.494
Cancer (prior)	2.06	0.22-19.11	.526	4.18	0.67-25.98	.125
Hypothyroidism	0.89	0.11-7.34	.916	2.72	0.67-11.06	.162
Autoimmune disease	-	-	-	2.33	0.70-7.79	.168
$pO_2 < 60$ mmHg	3.34	0.97-14.52	.056	2.09	0.83-5.29	.120
$pCO_2 > 45$ mmHg	0.56	0.07-4.47	.586	11.31	3.72-34.34	< .001
Hemoglobin, per 1 g/dL	0.69	0.56-0.84	< .001	0.92	0.76-1.11	.366
Leukocytes, per 1000	1.23	1.11-1.36	< .001	1.11	1.01-1.21	.027
Lymphocytes, per 100	0.90	0.51-1.61	.728	0.09	0.03-0.31	< .001
Platelets, per 100 000	1.20	0.84-1.72	.315	1.19	0.85-1.65	.307
Creatinine, per 1 g/dL	1.64	1.14-2.34	.007	1.51	1.08-2.10	.016
D-dimer, per 100 units	1.01	1.00-1.01	.049	1.00	0.99-1.00	.770
Ferritin, per 100 units	1.02	0.98-1.06	.473	1.05	1.02-1.09	.002
CRP, per unit	1.02	0.99-1.05	.068	1.05	1.02-1.08	.003
Interleukine-6, per unit	1.00	1.00-1.01	.358	1.01	1.00-1.01	.018
Antiplatelet therapy	1.37	0.48-3.89	.553	0.96	0.34-2.67	.941
Anticoagulation	10.83	4.30-27.24	< .001	5.56	2.31-13.56	< .001
ACEI/ARBs	1.22	0.53-2.79	.642	1.23	0.59-2.60	.580
Beta-blockers	5.08	2.13-12.12	< .001	2.71	1.17-6.26	.020
Corticosteroids	0.40	0.05-3.13	.385	1.06	0.30-3.84	.924

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; OSAHS, obstructive sleep apnea-hypopnea syndrome; pO_2, partial pressure of oxygen; SaO_2, oxygen saturation; TIA, transient ischemic attack. Unless otherwise indicated, the data are expressed as No. (%) or mean ± standard deviation.
Multivariate analyses were adjusted by those variables with a $P < .05$ value in the univariate analysis:
• Adjustment for mortality by age, sex, $SaO_2 < 95\%$, retirement home, dependency, diabetes mellitus peripheral artery disease, heart disease, atrial fibrillation prior stroke, chronic kidney disease, hemoglobin leukocytes, creatinine, D-dimer, anticoagulation, B-blockers.
• Adjustment for heart failure by: $SaO_2 < 95\%$, peripheral artery disease, ventricular dysfunction, atrial fibrillation, hypercapnia, leukocytes, lymphocytes, creatinine, ferritin, CRP, interleukine-6, anticoagulation, B-blockers.
• Adjustment for the combined of death and heart failure for: age, sex, $SaO_2 < 95\%$, retirement home, dependency, diabetes mellitus, peripheral artery disease, heart disease, atrial fibrillation, prior stroke/TIA, hypercapnia, hemoglobin, leukocytes, lymphocytes, creatinine, D-dimer, ferritin, CRP, IL-6, anticoagulation, beta-blockers.

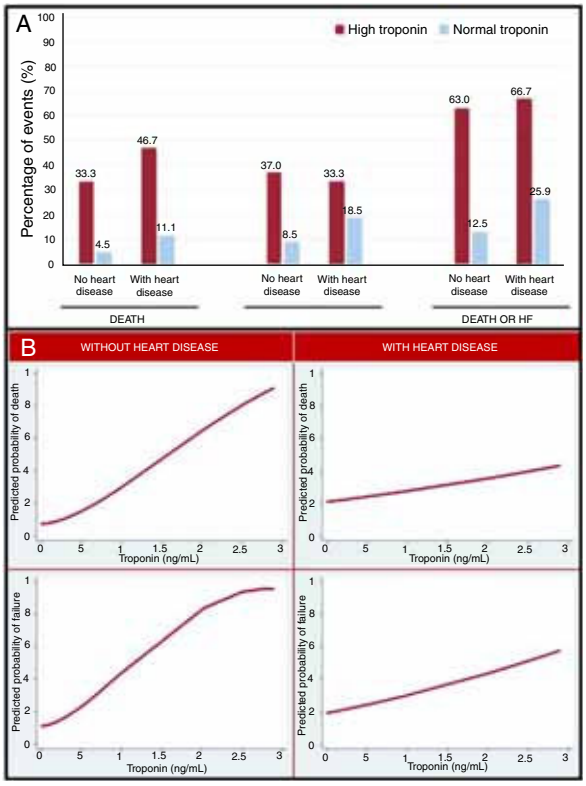

Figure 1. A: events in patients with high or normal troponin levels depending on whether or not they have heart disease. B: relationship between troponin and the predicted probability of death and heart failure according to the presence or not of heart disease. HF, heart failure.

with a worse prognosis. This predictive power of risk of death or HF was particularly significant in patients without previous HD. Based on these results, TnI determination should be routinely included in patients hospitalized for COVID-19.

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REFERENCES

1. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med.* 2020;382:1199–1207.
2. World Health Organization. WHO announces COVID-19 outbreak a pandemic. 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Consulted 20 Jul 2020.
3. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5:1–8.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506.
5. Bikdeli B, Madhavan MV, Jiménez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75:2950–2973.
6. Chapman AR, Bularga A, Mills NL. High-Sensitivity Cardiac Troponin Can Be an Ally in the Fight Against COVID-19. *Circulation.* 2020;141:1733–1735.

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Usefulness and safety of self-electrocardiographic monitoring during treatment with hydroxychloroquine and azithromycin in COVID-19 patients

Utilidad y seguridad de la automonitorización electrocardiográfica durante el tratamiento con hidroxicloroquina y azitromicina en pacientes con COVID-19

To the Editor,

Despite the lack of solid evidence on their efficacy, hydroxychloroquine (HCQ) and azithromycin (AZ) have been widely used as a first-line treatment for infection with SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19). The effect of these drugs on the QT interval and their potential to cause polymorphic ventricular arrythmias has generated growing concern in the scientific community and until more robust evidence on their usefulness is available, we must employ strategies to ensure their safe use.[1] Recently, the Food and Drug Administration recommended the use of noninvasive remote monitoring devices to facilitate the monitoring of these patients, which minimizes contact with health care professionals, reduces the burden on health care services and allows more efficient use of resources.[2] To this end, the KardiaMobile 6L device, from AliveCor (California, USA), has been proposed, which can provide a 1- or 6-lead electrocardiogram (ECG), offering a simple and reproducible way to determine the corrected QT interval (QTc).[3] Here in Spain, there are already protocols to support its use in these patients.[4]

During March and April of 2020, a study was conducted in our hospital to analyze the effect of treatment with HCQ (either alone or in combination with AZ) on the QTc and the incidence of ventricular arrhythmias in patients admitted with SARS-CoV-2 pneumonia who met the high-risk criteria for QTc prolongation (female, age > 65 years, history of heart disease, chronic renal disease, or diabetes, or taking both medications together). In line with the recommendations from the experts,[3] a protocol was designed to minimize the arrhythmic complications of these drugs. This protocol included a series of precautions to be taken before and during treatment: *a)* review what other medications the patient is taking that could prolong the QTc; *b)* correct electrolyte imbalances; *c)* avoid bradycardia; and *d)* perform close electrocardiographic monitoring. A baseline 12-lead ECG was performed on admission. Later, the QTc was monitored using a 6-lead recording taken with the KardiaMobile 6L device, at 48 hours and 96 hours after starting the drugs (or more often if the QTc was > 480 ms, if there was an increase > 60 ms, or if the patient had possible symptoms of arrythmia). The arrhythmia unit trained the nursing staff responsible for these patients using an informational video on the use of KardiaMobile 6L. After a brief explanation from the nursing staff, the patient performed the