

Cardiac troponin and COVID-19 severity: Results from BIOCOVID study

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Abstract

Background: Myocardial injury is a common finding in COVID-19 strongly associated with severity. We analysed the prevalence and prognostic utility of myocardial injury, characterized by elevated cardiac troponin, in a large population of COVID-19 patients, and further evaluated separately the role of troponin T and I.

Methods: This is a multicentre, retrospective observational study enrolling patients with laboratory-confirmed COVID-19 who were hospitalized in 32 Spanish hospitals. Elevated troponin levels were defined as values above the sex-specific 99th percentile upper reference limit, as recommended by international guidelines. Thirty-day mortality was defined as endpoint.

Results: A total of 1280 COVID-19 patients were included in this study, of whom 187 (14.6%) died during the hospitalization. Using a nonspecific sex cut-off, elevated troponin levels were found in 344 patients (26.9%), increasing to 384 (30.0%) when a sex-specific cut-off was used. This prevalence was significantly higher (42.9% vs 21.9%; $P < .001$) in patients in whom troponin T was measured in comparison with troponin I. Sex-specific elevated troponin levels were significantly associated with 30-day mortality, with adjusted odds ratios (ORs) of 3.00 for total population, 3.20 for cardiac troponin T and 3.69 for cardiac troponin I.

Conclusion: In this multicentre study, myocardial injury was a common finding in COVID-19 patients. Its prevalence increased when a sex-specific cut-off and cardiac troponin T were used. Elevated troponin was an independent predictor of 30-day

mortality, irrespective of cardiac troponin assay and cut-offs to detect myocardial injury. Hence, the early measurement of cardiac troponin may be useful for risk stratification in COVID-19.

KEYWORDS

cardiac troponin I, cardiac troponin T, COVID-19, myocardial injury, prognosis, SARS-CoV-2

1 | INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the aetiological agent for the pneumonia cases of unknown origin in Wuhan (Hubei Province, China), a disease designated as coronavirus disease 2019 (COVID-19)¹ and characterized as pandemic in March 11th.

Although the predominant clinical manifestation of COVID-19 is viral pneumonia,^{2,3} SARS-CoV-2 infection can also cause extrapulmonary manifestations and complications, including cardiovascular disorders, such as acute myocardial injury, which is strongly associated with mortality.⁴ Coronavirus-associated acute myocarditis, angiotensin-converting enzyme 2 receptor binding affinity to the virus Spike protein, increased cytokine secretion and hypoxia-induced cardiac myocyte apoptosis have been identified as potential mechanisms of myocardial tissue damage.⁵

The role of laboratory medicine in this viral outbreak includes prognostication of COVID-19 patients.⁶ Cardiac troponin is a well-known marker of myocardial injury.⁷ Previous recent studies have demonstrated the association of myocardial injury, characterized by elevated cardiac troponins, with COVID-19 severity in Western multicentre cohorts⁸ and single-centre studies,^{9,10} and its measurement has been recommended for prognosis of these patients as indicative of a worsening clinical scenario.^{11,12} However, to our knowledge, no study has evaluated the implications of using sex-specific thresholds, as recommended,¹³ to define myocardial injury.

In this study, we aimed to analyse the prevalence of myocardial injury based on the type of cardiac troponin (I or T) and the cut-off points for its detection. Furthermore, we evaluated the association of myocardial injury, characterized by increased baseline troponin levels, measured within 24 hours from admission to the emergency department (ED), and 30-day mortality, in a large cohort including patients who were admitted to 32 hospitals in Spain. We analysed this prognostic value according to two thresholds to define myocardial injury: 99th percentile and sex-specific 99th percentile upper reference limit.

2 | MATERIALS AND METHODS

2.1 | Design

BIOCOVID study is a multicentre, retrospective observational study enrolling patients hospitalized with a diagnosis of COVID-19 and recruited in 32 hospitals of Health National System in 9 autonomous communities of Spain. The recruitment period was from 1 March 2020 to 30 April 2020. The follow-up censoring date was 20 May 2020.

Because of the retrospective design, we received the approval for data collection with waiver of informed consent.

This study was endorsed by Spanish Association of Medical Biopathology and Laboratory Medicine (AEBM-ML), Spanish Association of Clinical Laboratory (AEFA) and Spanish Society of Laboratory Medicine (SEQC-ML).

2.2 | Study population

All consecutive adult patients (≥ 14 years) discharged or dead after hospital admission, with SARS-CoV-2 infection, were eligible for enrolment in the study. COVID-19 was diagnosed by a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing of a nasopharyngeal specimen.

Exclusion criteria were as follows: (a) patients <14 years; (b) pregnant women; (c) patients transferred from or to other hospital; (d) patients transferred from nursing homes; (e) patients discharged from the ED for at home treatment; (f) patients with intensive care unit (ICU) admission criteria who were not admitted due to lack of availability; and (g) patients in whom troponin was not measured within 24 hours from admission to ED or it was measured using a contemporary assay.

2.3 | Laboratory assays for troponin measurement

A value above the 99th percentile upper reference limit of a normal reference population is the recommended threshold

which defines an increased cardiac troponin indicative of myocardial injury.⁷ Sex-specific and non-sex-specific cardiac troponin thresholds, according to manufacturer's data, for detection of myocardial injury, are described in Table S1.

2.4 | Data collection

Data collection was performed retrospectively from electronic medical records and laboratory information systems by two researchers for each hospital. For eligible patients, we extracted the demographic information, comorbidities and laboratory test results, including cardiac troponin. We defined baseline laboratory testing as the first result available within 24 hours from admission to ED. A multicentre database was prepared for register of collected data, and all patient identities were coded for blindness.

2.5 | Statistical analysis

Continuous variables were checked for normal distribution using the Kolmogorov-Smirnov's test. Data were described as numbers and percentages for categorical variables and or medians with interquartile ranges (IQRs) for continuous data. Comparisons between groups were performed with chi-squared test for categorical data and Mann-Whitney U tests for continuous data.

For survival analysis, time zero was defined as the time of admission to ED. In order to assess survival probability by Kaplan-Meier method and log-rank test, with the endpoint being 30-day all-cause mortality, the study population was divided according to the presence of myocardial injury, defined by elevated cardiac troponin levels. The association of baseline cardiac troponin levels with the endpoint was assessed by binary logistic regression, adjusting for age, gender, prior comorbidities, glomerular filtration rate (GFR) and the other biomarkers included in the study. We further investigated the relative importance of each of the covariates entered in the final multivariable model by mean of the analysis of the χ^2 score. Statistical significance was set at 5%. SPSS software version 20 (IBM Corporation, USA) was used for statistical analyses.

Reporting of the study conforms to CONSORT-revised and the broader EQUATOR guidelines.¹⁴

3 | RESULTS

During the study period, a total of 2981 COVID-19 patients admitted to 32 Spanish hospitals were recruited. One-hundred and eight patients who were still hospitalized on May 20, 2020, were excluded for analyses. According

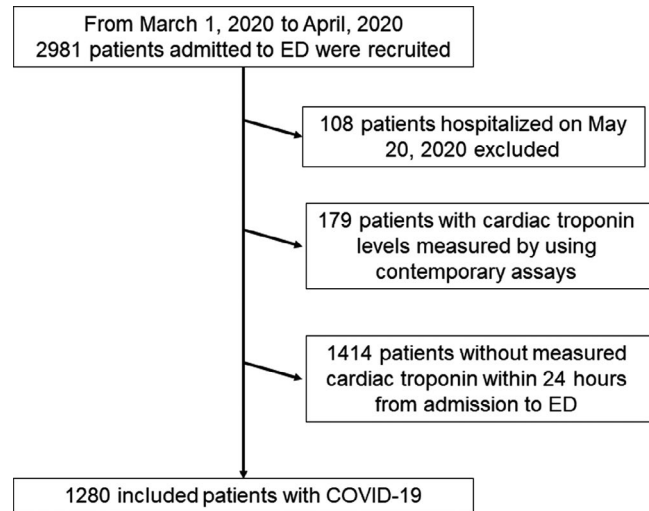


FIGURE 1 Flow chart of patient recruitment

to exclusion criteria, 179 patients were excluded because troponin levels were measured by using contemporary assays and 1414 because troponin levels were not available within 24 hours from admission to ED. The study population finally included 1280 hospitalized COVID-19 patients [median age (IQR): 67 years, 750 male patients (58.6%)] (Figure 1). The most common comorbidity was hypertension (45.4%), followed by prior cardiovascular disease (25.6%) and diabetes mellitus (24.1%). Thirty-day mortality rate was 14.6% and 249 patients required ICU admission (19.5%).

3.1 | Characteristics of the study population depending on cardiac troponin assay

Troponin levels were measured by using a cardiac troponin T assay (TnT group) in 494 (38.6%) patients and a cardiac troponin I assay (TnI group) in 786 (61.4%). Thirty-day mortality was similar in both groups (12.8% vs 15.5%, $P = .136$), and no significant differences were observed between both groups with regard to demographics and comorbidities (Table 1).

Cardiac troponin levels above 99th percentile were found in 344/1280 (26.9%) patients, increasing slightly to 30% (384/1280) when sex-specific 99th percentile was used to define myocardial injury. The percentage of patients with cardiac troponin I above 99th percentile was significantly lower compared to cardiac troponin T (20.2% vs 37.4%; $P < .001$). This observation was also true when sex-specific cut-off values were used (troponin I vs troponin T, 21.9% vs 42.9%; $P < .001$). Finally, we analysed the percentage of patients with elevated cardiac troponin levels according to sex and cut-off; both in overall, TnT and TnI groups, the percentage of patients with elevated cardiac troponin levels was higher for women and lower for men when sex-specific cut-offs

TABLE 1 Characteristics of study population according to assay for measurement of cardiac troponin

Variable	All population	TnT group	TnI group	P-value
n (%)	1280	494 (38.6)	786 (61.4)	
Age, years	67 (55-77)	67 (54-77)	67 (56-77)	.740
Gender, male	750 (58.6)	287 (58.1)	463 (58.9)	.775
30-day mortality, n (%)	187 (14.6)	63 (12.8)	124 (15.5)	.136
Troponin > p99th, n (%)	344 (26.9)	185 (37.4)	159 (20.2)	<.001
Troponin > sex-specific p99th, n (%)	384 (30.0)	212 (42.9)	172 (21.9)	<.001
Hypertension, n (%)	581 (45.4)	214 (43.3)	367 (46.7)	.238
Diabetes mellitus, n (%)	309 (24.1)	120 (24.3)	189 (24.0)	.920
Cardiovascular disease, n (%)	328 (25.6)	118 (23.9)	210 (26.7)	.259
COPD, n (%)	114 (8.9)	44 (8.9)	7.0 (8.9)	.999
Chronic kidney disease, n (%)	103 (8.0)	37 (7.5)	66 (8.4)	.561

Note: Continuous variables as median (IQR).

Abbreviations: COPD, chronic obstructive pulmonary disease.

were used for classifying the patients (data summarized in Table S2).

Comparisons for demographics, comorbidities and laboratory findings between patients with normal and elevated cardiac troponin levels are shown in Table 2. Thirty-day mortality, but not ICU admission, was significantly higher in patients with myocardial injury, irrespective of the cardiac troponin cut-off used for its detection. Compared with those with cardiac troponin values below upper limit, patients with elevated cardiac troponin levels were older and commonly male and showed a higher prevalence of hypertension, cardiovascular disease, chronic kidney disease and diabetes mellitus. Laboratory tests showed higher lactate dehydrogenase (LDH), C-reactive protein (CRP) and D-dimer levels and lower GFR and lymphocyte count in patients with elevated cardiac troponin levels, regardless of the cut-off used to detect myocardial injury. Only patients with increased cardiac troponin levels according to an overall cut-off showed a significant lower platelet count.

3.2 | Characteristics of the study population: elevated cardiac troponin levels on admission and 30-day mortality

Characteristics of study population according to 30-day mortality are summarized in Table 3. Compared to survivors, nonsurvivors were older and commonly male and presented an increased prevalence of comorbidities; regarding to laboratory tests, LDH, CRP and D-dimer levels were higher and GFR and lymphocyte and platelet counts were lower in patients who died. Besides, the percentage of patients with myocardial

injury, according to cardiac troponin levels, nonspecific or sex-specific, was significantly higher in nonsurvivors.

In a Kaplan-Meier analysis, baseline cardiac troponin levels above 99th percentile or sex-specific 99th percentile upper reference limit were associated with increased 30-day mortality (Figure 2). In multivariate binary logistic regression analysis, the odds ratios (ORs) for patients with cardiac troponin levels, irrespective of cut-off points used to define myocardial injury, remained significant after adjusting for confounders (Table 5).

3.3 | Cardiac troponin T and troponin I: association with 30-day mortality

Given that the percentage of patients classified as having myocardial injury was significantly higher in TnT group, we analysed separately the association of elevated cardiac troponin levels with death according to cardiac troponin assay. Characteristics of both groups stratified according to survival are summarized in Table 4. In both, compared to survivors, nonsurvivors were older, and only in TnI group commonly male. Regarding to comorbidities, nonsurvivors presented an increased prevalence of hypertension, diabetes mellitus, cardiovascular disease and chronic kidney disease; only in TnT group, the prevalence of COPD was higher in patients who died. Finally, when laboratory tests were compared, LDH, CRP and D-dimer levels were higher and GFR, lymphocyte and platelet counts were lower in patients who died.

An elevated cardiac troponin level was also significantly more common in nonsurviving patients. It is noteworthy that the percentage of deceased patients with elevated troponin

TABLE 2 Demographics, preexisting comorbidities and laboratory tests stratified by cardiac troponin on admission to ED (n = 1280)

Variable	Troponin (99th percentile)		P-value	Troponin (Sex-specific 99th percentile)		P-value
	Normal	Elevated		Normal	Elevated	
n (%)	936 (73.1)	344 (26.9)		896 (70)	384 (30.0)	
Demographics						
Age, years	63 (51-72)	78 (69-85)	<0.001	62 (51-71)	77 (69-85)	<.001
Age > 50 years	714 (76.3)	334 (97.1)	<0.001	680 (75.9)	368 (95.8)	<.001
Gender, male	529 (56.5)	221 (64.2)	0.013	553 (61.7)	197 (51.3)	.001
Outcomes						
30-day mortality	78 (8.3)	109 (31.7)	<0.001	76 (8.5)	111 (28.9)	<.001
ICU admission	174 (18.6)	75 (21.8)	0.198	174 (19.4)	75 (19.5)	.963
Comorbidities						
Hypertension, n (%)	358 (38.2)	223 (64.8)	<0.001	335 (37.4)	246 (64.1)	<.001
Diabetes mellitus, n (%)	198 (21.2)	111 (32.3)	<0.001	185 (20.6)	124 (32.3)	<.001
Cardiovascular disease, n (%)	178 (19.0)	150 (43.6)	<0.001	168 (18.8)	160 (41.7)	<.001
COPD, n (%)	73 (7.8)	41 (11.9)	0.022	71 (7.9)	43 (11.2)	.060
Chronic kidney disease, n (%)	39 (4.2)	64 (18.6)	<0.001	38 (4.2)	65 (16.9)	<.001
Laboratory findings						
CRP (mg/dL) (n = 1274)	7.9 (3.4-13.8)	10.2 (5.2-17.0)	<0.001	8.1 (3.4-14.4)	9.5 (4.6-16.3)	.005
GFR (mL/min/1.73 m ²) (n = 1278)	87 (70-101)	60 (40-82)	<0.001	87 (70-101)	62 (42-83)	<.001
LDH (U/L) (n = 1185)	294 (230-389)	347 (248-472)	<0.001	297 (230-390)	337 (242-458)	<.001
D-dimer (ng/mL FEU) (n = 1257)	645 (410-1101)	1080 (591-2077)	<0.001	646 (410-1100)	986 (555-2007)	<.001
Lymphocyte count (*10 ⁹ /L) (n = 1280)	1.00 (0.70-1.319)	0.88 (0.60-1.27)	<0.001	0.98 (0.70-1.31)	0.90 (0.60-1.30)	.009
Platelet count (*10 ⁹ /L) (n = 1280)	200 (159-265)	192 (145-250)	0.024	199 (158-262)	198 (148-252)	.226

Note: Continuous variables as median (IQR).

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ED, emergency department; GFR, glomerular filtration rate; ICU, intensive care unit; LDH, lactate dehydrogenase.

levels was higher in TnT group in comparison with TnI group (76.2% vs 49.2% using an overall cut-off and 79.4% vs 49.2% using a sex-specific cut-off).

For both troponin T and I, elevated baseline levels were associated with increased 30-day mortality (Figures 3 and 4). Both types of cardiac troponin, T and I, were also independent predictors for 30-day mortality, after adjusting for confounders (Table 5).

Finally, when we investigated the relative importance of each of the covariates entered in the final multivariable model, the information yielded by cardiac troponin levels, irrespective of the cut-off, 99th percentile or sex-specific 99th percentile, was the most powerful in the final model to predict 30-day all-cause mortality. This finding was also consistent when only cardiac troponin I was analysed. Cardiac troponin T was the second most powerful predictor of 30-day mortality after GFR (Table 5).

4 | DISCUSSION

Our study supports the concept that acute myocardial injury, determined by elevated cardiac troponin levels, is a common finding in patients hospitalized for COVID-19.⁴ This biomarker is related but not limited to myocardial injury. Its elevation during COVID-19 infection is likely to be multifactorial, and it is not only attributable to atherothrombotic coronary occlusion and might be related with an increase of the prevalence of nonischaemic myocardial injury and type 2 myocardial infarction in SARS-CoV-2-infected patients with a significant respiratory compromise.

The role of cardiac troponin for management of patients with COVID-19 is controversial, and it is a matter of ongoing debate whether troponin T or I should be measured as a prognostic marker. European Society of Cardiology (ESC) recognizes that the strong and consistent association

TABLE 3 Characteristics of patients in total population grouping by survival status

Variable	Survivors	Nonsurvivors	P-value
n (%)	1093 (85.4)	187 (14.6)	
Demographics			
Age, years	64 (54-75)	77 (68-83)	<.001
Age > 50 years	866 (79.2)	182 (97.3)	<.001
Gender, male	615 (56.3)	135 (72.2)	<.001
Comorbidities			
Hypertension, n (%)	451 (41.3)	130 (69.5)	<.001
Diabetes mellitus, n (%)	243 (22.2)	66 (35.3)	<.001
Cardiovascular disease, n (%)	253 (23.1)	75 (40.1)	<.001
COPD, n (%)	91 (8.3)	23 (12.3)	.078
Chronic kidney injury, n (%)	67 (6.1)	36 (19.3)	<.001
Laboratory findings			
Troponin > p99th, n (%)	235 (21.5)	109 (58.3)	<.001
Troponin > sex-specific p99th, n (%)	273 (25.0)	111 (59.4)	<.001
CRP (mg/dL)	7.7 (3.3-13.6)	14.2 (8.5-20.3)	<.001
GFR (mL/min/1.73 m ²)	84 (65-100)	60 (39-78)	<.001
GFR < 60 mL/min/1.73 m ² , n (%)	208 (19.1)	98 (40.1)	<.001
LDH (U/L)	294 (230-389)	378 (287-546)	<.001
D-dimer (ng/mL FEU)	699 (428-1202)	1102 (548-2090)	<.001
Lymphocyte count (*10 ⁹ /L)	1.00 (0.70-1.33)	0.80 (0.56-1.10)	<.001
Platelet count (*10 ⁹ /L)	200 (158-265)	179 (138-234)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GFR, glomerular filtration rate; LDH, lactate dehydrogenase.

of troponin with death in patients infected by SARS-CoV-2 reported in the literature should be seen in favour of this approach, but it concludes that, at this point of time, it is unlikely that cardiac troponin provides incremental value to a predictive model including other strong predictors of death, such as older age, D-dimer or lymphocyte count and that no specific therapeutic intervention can be justified based on the use of cardiac troponin as a prognostic marker.¹⁵ However, the measurement of cardiac troponin for prognosis of severity in patients with COVID-19 is supported in other international guidelines and expert recommendations.^{11,16} Hence, taken together with electrocardiogram and the clinical assessment, elevation of cardiac troponin levels can inform about ischaemic and nonischaemic causes of myocardial injury related to COVID-19, which may be associated with a poorer prognosis.¹⁷

There is a growing evidence regarding the prevalence and prognostic role of myocardial injury in patients hospitalized with COVID-19. In our cohort, elevated troponin levels were found in 26.9% of the patients and in 30% when sex-specific cut-offs were used to detect myocardial injury, similar percentages to those recently reported in other multicentre studies including different assays for troponin.¹⁸ Besides, we described that, depending on the cardiac troponin assay (I or

T), the percentage of patients with myocardial injury was significantly lower in TnI group in comparison with TnT group (20.2% vs 37.4%), similar percentages to those recently reported in Spain by Bardají et al¹⁹ (22%) and Lorente-Ros et al²⁰ (20.9%) using assays for cardiac troponin I and Calvo-Fernández et al using cardiac troponin T (34.6%).⁹ This difference even remained when a sex-specific cut-off was used (21.9% vs 42.9%) and it would be related to different analytical sensitivities among the cardiac troponin assays used in this study for cardiac troponin measurement. High-sensitivity designation has been assigned to assays that are able to measure cardiac troponin levels precisely at or below the 99th percentile value and by an analytical sensitivity defined by a percentage of 50% or more detectable values above the limit of detection in a healthy reference population in both genders.¹³ However, doubts have been expressed that some high-sensitivity cardiac troponin assays fail to meet these criteria.²¹ Hence, Giannitsis et al²² have recently reported in a well-phenotyped healthy cohort that contrary to high-sensitivity cardiac troponin T, high-sensitivity cardiac troponin I on an ARCHITECTi2000_{SR} did not fulfil criteria for high-sensitivity designation for both genders. Yang et al²³ concluded that implementation of a high-sensitivity cardiac troponin I assay would not lead to an increase in the

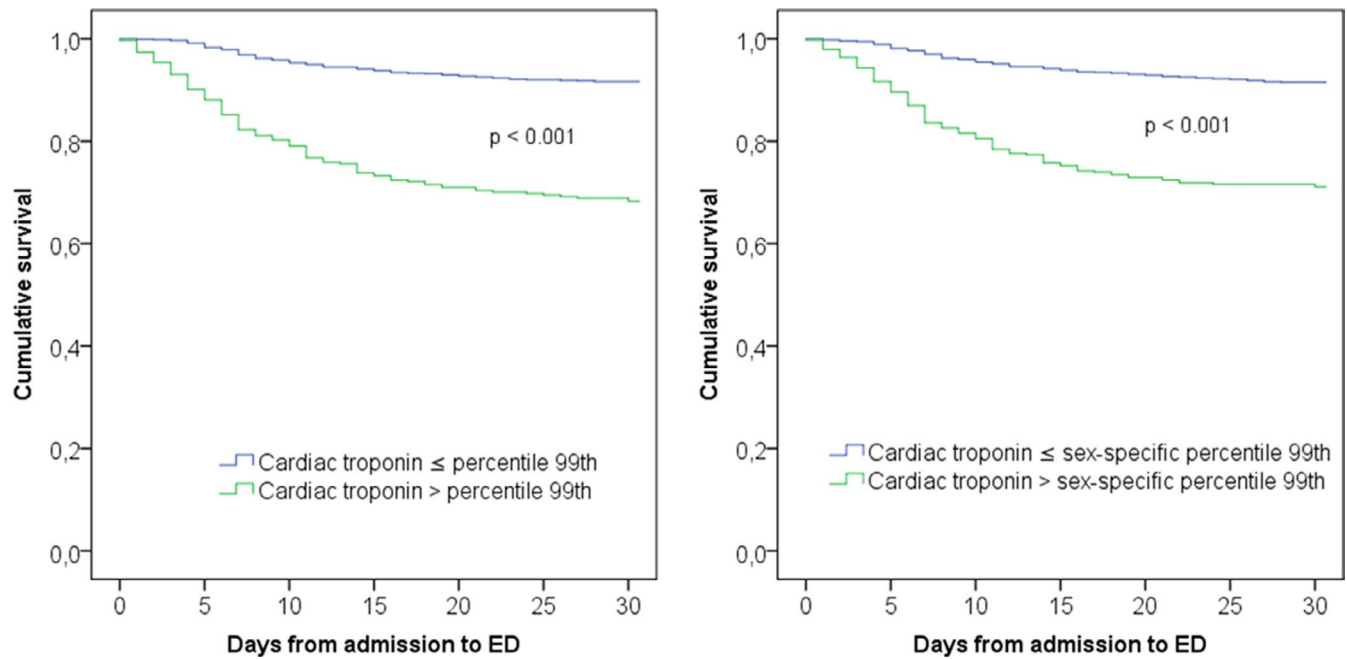


FIGURE 2 Cumulative incidence of 30-day mortality during hospitalization stratified by baseline cardiac troponin level

TABLE 4 Characteristics of TnT group and TnI group according to survival status

Variable	TnT group (n = 494)		P-value	TnI group (n = 786)		P-value
	Survivors	Nonsurvivors		Survivors	Nonsurvivors	
n (%)	431 (87.2)	63 (12.8)		662 (84.2)	124 (15.8)	
Demographics						
Age, years	64 (53-74)	79 (72-86)	<0.001	65 (54-75)	77 (68-75)	<.001
Age > 50 years	335 (77.7)	63 (100)	<0.001	531 (80.2)	119 (96)	<.001
Gender, male	244 (56.6)	43 (68.3)	0.080	371 (56.0)	92 (74.2)	<.001
Comorbidities						
Hypertension, n (%)	170 (39.4)	44 (69.8)	<0.001	281 (42.4)	86 (69.4)	<.001
Diabetes mellitus, n (%)	98 (22.7)	22 (34.9)	0.035	145 (25.9)	44 (35.5)	.001
Cardiovascular disease, n (%)	91 (21.1)	27 (42.9)	<0.001	162 (24.5)	48 (38.7)	.001
COPD, n (%)	34 (7.9)	10 (15.9)	0.038	57 (8.6)	13 (10.5)	.501
Chronic kidney disease, n (%)	22 (5.1)	15 (23.8)	<0.001	45 (6.8)	21 (16.9)	<.001
Laboratory findings						
Troponin > p99th, n (%)	137 (31.8)	48 (76.2)	<0.001	98 (14.8)	61 (49.2)	<.001
Sex-specific Troponin > p99th, n (%)	162 (37.6)	50 (79.4)	<0.001	111 (16.8)	61 (49.2)	<.001
CRP (mg/dL)	6.6 (2.6-12.8)	15.0 (10.0-23.0)	<0.001	8.4 (3.6-14.1)	13.6 (8.4-19.9)	<.001
GFR (mL/min/1.73 m ²)	81 (63-96)	55 (33-71)	<0.001	86 (67-103)	63 (44-85)	<.001
GFR < 60 mL/min/1.73 m ² , n (%)	85 (19.8)	36 (57.1)	<0.001	123 (18.6)	70 (56.5)	<.001
LDH (U/L)	282 (221-377)	274 (375-476)	<0.001	303 (237-395)	389 (289-573)	<.001
D-dimer (ng/mL FEU)	721 (437-1390)	1300 (725-2679)	<0.001	681 (420-1161)	979 (523-1806)	<.001
Lymphocyte count (*10 ⁹ /L)	1.04 (0.75-1.46)	0.65 (0.50-1.28)	<0.001	0.90 (0.70-1.20)	0.80 (0.60-1.10)	<.001
Platelet count (*10 ⁹ /L)	197 (162-274)	185 (139-227)	0.005	198 (156-255)	178 (134-239)	.005

Abbreviations: and CRP: C-reactive protein; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; LDH: lactate dehydrogenase.

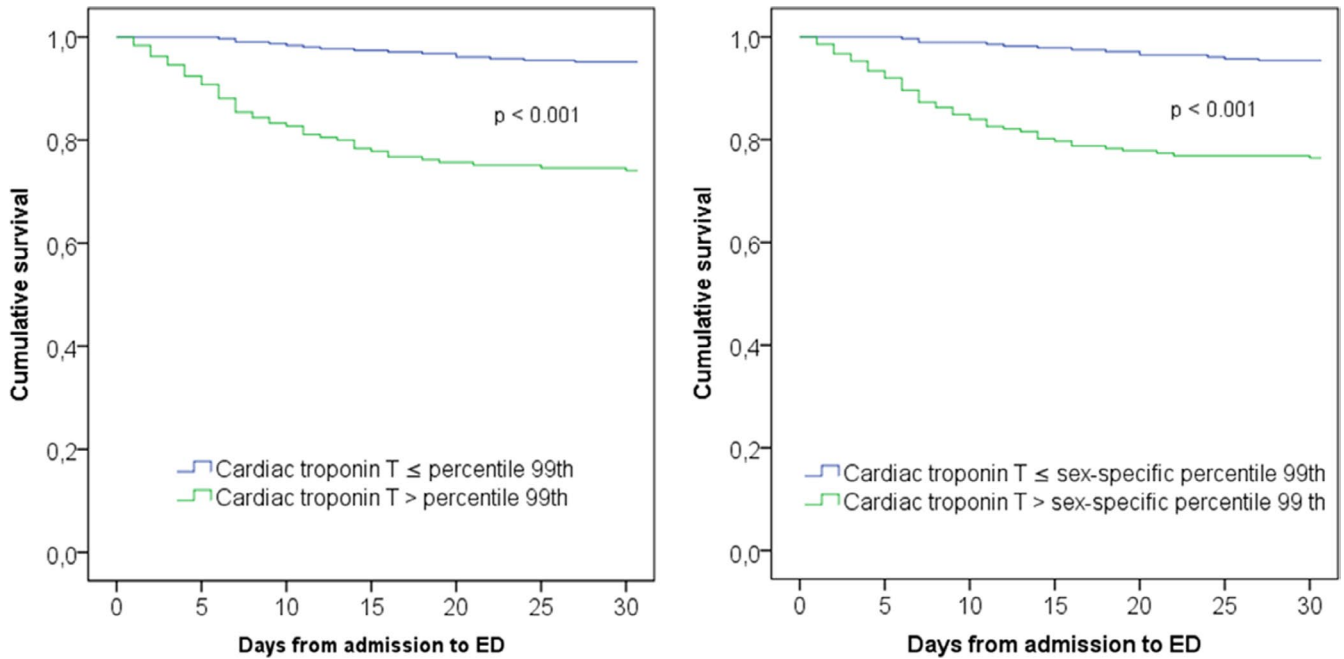


FIGURE 3 Cumulative incidence of 30-day mortality during hospitalization stratified by baseline cardiac troponin T level

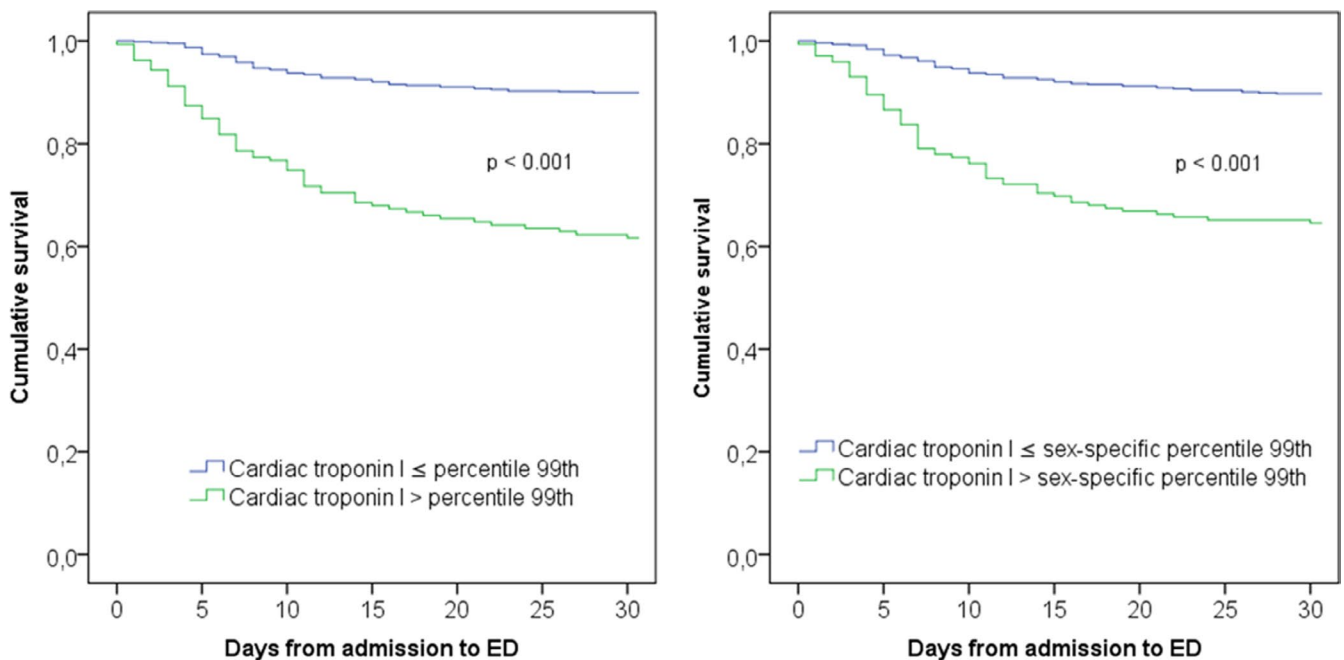


FIGURE 4 Cumulative incidence of 30-day mortality during hospitalization stratified by baseline cardiac troponin I level

proportion of elevated cardiac troponin levels above the 99th percentile.

To our knowledge, this is the first study reporting variations in the prevalence of myocardial injury, defined by elevated cardiac troponin levels, due to the use of sex-specific cut-offs. Differences in cardiac troponin levels depending on sex have been previously described, with levels significantly higher in men compared to women.^{24,25} It is probable that

using an overall cut-off, the prevalence of myocardial injury is underestimated for women and overestimated for men.²⁴ Hence, Kavsak et al have also recommended sex-specific upper reference limits for high-sensitivity cardiac troponin assays when used for prognosis of COVID-19 patients.¹⁶ In our cohort, using this cut-off, the percentage of elevated troponin levels increased slightly from 26.9% to 30% in overall population, from 37.4% to 42.9% in TnT group and from

TABLE 5 Association between troponin cut-offs and 30-day mortality

	Adjusted OR ^a (95% CI)	AUC full model	Contribution to AUC	χ^2	Relative importance
Troponin > 99th percentile	2.99 (2.03-4.41)	0.80 (0.77-0.84)	0.028 (0.027-0.029)	104.6	1
Troponin > sex-specific 99th percentile	3.00 (2.03-4.44)	0.81 (0.77-0.84)	0.031 (0.029-0.033)	84.4	1
Troponin T > 99th percentile	2.91 (1.38-6.17)	0.85 (0.80-0.89)	0.017 (0.012-0.021)	39.4	2 ^b
Troponin T > sex-specific 99th percentile	3.20 (1.46-7.05)	0.84 (0.79-0.88)	0.006 (0.004-0.007)	33.4	2 ^b
Troponin I > 99th percentile	3.76 (2.31-6.11)	0.80 (0.75-0.84)	0.035 (0.034-0.035)	76.8	1
Troponin I > sex-specific 99th percentile	3.69 (2.27-6.00)	0.80 (0.76-0.84)	0.037 (0.035-0.040)	63.6	1

Note: Relevance of troponin within the multivariable model as predictor.

Abbreviations: AUC, area under the curve; CI, confidence interval; OR, odds ratio.

^aAdjusted by age, sex, hypertension, diabetes, COPD, cardiovascular disease, chronic kidney disease, GFR, LDH, CRP, D-dimer, lymphocyte and platelet counts. Dependent variable is 30-day mortality.

^bGFR is the most important predictor ($\chi^2 = 41.0$).

20.2% to 21.9% in TnI group. Besides, the percentages of female and male patients with elevated cardiac troponin T or I levels increased and decreased, respectively, in comparison with those achieved with an overall cut-off. It could allow a substantial reclassification information for prediction of severity in COVID-19, as reported in other settings.²⁶

The effect of SARS-CoV-2 infection on myocardial function is not well established, and there are multiple factors explaining the increase in troponin levels in COVID-19 patients.²⁷ Although some cases of COVID-19 with fulminant myocarditis have been reported,²⁸ in most of the cases, the myocardial injury would be related to the inflammation and oxidative stress by cytokine storm, causing coagulopathy, microangiopathy and alterations in blood flow.²⁹ Finally, the myocardial oxygen supply-demand imbalance during infection, causing a type 2 myocardial infarction, would be another explanation for myocardial tissue damage.²⁹ This study also confirms the association of increased cardiac troponin levels and COVID-19 severity. Overall cardiac troponin, cardiac troponin T and cardiac troponin I were independent predictors for 30-day mortality, irrespective of cut-off points chosen for myocardial injury. This association has been previously described,^{8-10,16,30,31} although one of the main limitations of many studies evaluating the role of cardiac troponin for COVID-19 prognosis is the lack of data about the assays and their analytical characteristics, as well as the cut-offs to detect myocardial injury.¹⁶

4.1 | Strengths and limitations

To date, our study is one of the largest to describe patterns of cardiac injury in Europe. The main limitation of this

multicentre study is the retrospective design, subject to the limitations of this type of design, including selection bias, errors in data entry and residual confounding; cardiac troponin levels were not measured in all the patients, which may impact the strength of the association between the biomarker and mortality. Second, this is a multicentre study including assays for cardiac troponin I with different analytical characteristics and cut-off points to detect myocardial injury, criteria for high-sensitivity assay designation¹³; hence, we only classified the patients as those with normal or increased cardiac troponin levels, without the possibility of assessing the association between different values and severity. Recently, Quin et al³⁰ reported that the cut-offs of cardiac troponin for effective prognosis of 28-day mortality of COVID-19 were much lower than currently recommended thresholds for regular heart disease. Third, other cardiac markers, such as natriuretic peptides, which have demonstrated their prognostic value in combination with cardiac troponin,³² were not included in the study. Finally, serial measurements of cardiac troponin, which may provide additional data to stratify risk, were not available.³³

In conclusion, myocardial injury, characterized by elevated serum troponin levels, was a common finding in our study. This prevalence increased when cardiac troponin T was used to detect myocardial injury and also when a sex-specific cut-off was used. The use of 99th percentile sex-specific upper reference limits as surrogate would allow the detection of cardiac damage in a higher number of COVID-19 patients. Besides, using sex-specific cut-offs, the percentage of patients with myocardial injury decreased in male and increased in female; hence, using an overall cut-off could lead to a misclassification of patients. Finally, elevated increased serum troponin levels were associated with 30-day mortality,

irrespective of the type of cardiac troponin and the cut-off points to detect myocardial injury. The early measurement of cardiac troponin levels may be useful for risk stratification in patients infected by SARS-CoV-2, identifying a subgroup of patients with myocardial damage and a high risk of adverse events.


CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

AUTHORS' CONTRIBUTIONS

LGGR conceived and designed the study and supervised the conduct of the trial and data collection. LGGR and LCS analysed the data. LGGR drafted the article, and LCS, DMG and ORF contributed substantially to its revision. All the authors contributed to data collection in the participating hospitals and final approval of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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