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Prehospital troponin as a predictor of early clinical deterioration

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Abstract

Background and Objectives: Elevated troponin T (cTnT) values are associated with comorbidities and early mortality, in both cardiovascular and noncardiovascular diseases. The objective of this study is to evaluate the prognostic accuracy of the sole utilization of prehospital point-of-care cardiac troponin T to identify the risk of early in-hospital deterioration, including mortality within 28 days.

Methods: We conducted a prospective, multicentric, controlled, ambulance-based, observational study in adults with acute diseases transferred with high priority by ambulance to emergency departments, between 1 January and 30 September 2020. Patients with hospital diagnosis of acute coronary syndrome were excluded. The discriminative power of the predictive cTnT was assessed through a discrimination model trained using a derivation cohort and evaluated by the area under the curve of the receiver operating characteristic on a validation cohort.

Results: A total of 848 patients were included in our study. The median age was 68 years (25th-75th percentiles: 50-81 years), and 385 (45.4%) were women. The

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Transparency declaration: The corresponding author on behalf of the other authors guarantees the accuracy, transparency and honesty of the data and information contained in the study, that no relevant information has been omitted and that all discrepancies between authors have been adequately resolved and described.

The study is registered in the WHO International Clinical Trials Registry Platform (ICTRP) with number [ISRCTN48326533]. Details of the study design, statistical analysis plan and raw data are available online (doi.org/10.1186/ISRCTN48326533).

mortality rate within 28 days was 12.4% (156 cases). The predictive ability of cTnT to predict mortality presented an area under the curve of 0.903 (95% CI: 0.85-0.954; $P < .001$). Risk stratification was performed, resulting in three categories with the following optimal cTnT cut-off points: high risk greater than or equal to 100, intermediate risk 40-100 and low risk less than 40 ng/L. In the high-risk group, the mortality rate was 61.7%, and on the contrary, the low-risk group presented a mortality of 2.3%.
Conclusions: The implementation of a routine determination of cTnT on the ambulance in patients transferred with high priority to the emergency department can help to stratify the risk of these patients and to detect unknown early clinical deterioration.

KEYWORDS
ambulance, biomarkers, clinical prediction rule, medical decision-making, prehospital emergency care

1 | INTRODUCTION

Cardiovascular diseases, particularly those of coronary origin, are one of the leading causes of mortality in developed countries.[1] To efficiently identify patients with short-term cardiovascular risk, several biomarkers have begun to be routinely used in most hospitals; due to their high sensitivity,[2] cardiac troponin (cTnT) and more recently troponin I are two examples of such biomarkers already employed. As it has been demonstrated, elevated levels of cTnT imply myocardial damage which has been related to worst prognosis in cardiovascular disease,[3] being the biomarker of choice in acute coronary syndromes.[4]

High cTnT values are associated with both cardiovascular and noncardiovascular comorbidities, with the subsequent serious adverse events.[5] Troponinaemia, classically considered as an unimportant alteration once an acute coronary disease has been ruled out, requires patient's follow-up and study to find the causes that generate myocardial suffering.[6,7] For instance, values of cTnT greater than 30 ng/L may indicate demand ischaemia in the context of other serious pathologies (eg heart failure, pulmonary embolism, major trauma, kidney failure, sepsis, shock, ischaemic stroke).[8,9] In the prehospital care context, values of cTnT ≥50 ng/L correlate with a worse prognosis, regardless of the final diagnosis.[10-12]

The objective of this study was to determine the prognostic accuracy of the sole utilization of prehospital point-of-care cardiac troponin to identify the risk of early in-hospital deterioration, including mortality within 28 days after the index event. As a secondary objective, the implication of sex, age and pathology on troponin performance was also explored.

2 | METHODS

2.1 | Design and setting

We conducted a prospective, multicentric, controlled, ambulance-based, observational study in adults with acute disease transferred with high priority by ambulance to emergency departments (ED), between 1 January and 30 September 2020.

The study was carried out in a province with a reference population of 524,204 inhabitants, involving fourteen basic life support (BLS) teams and one advanced life support (ALS), which referred patients to two tertiary university hospitals of the Public Health System of Castilla-León (Spain).

Citizens requesting help to the telephone number 1-1-2 are assisted by an operator who collects filiation and geolocation data; after a quick interview with key questions, a coordinator physician selects the most appropriate care resource. The ALS team is composed of an emergency physician, an emergency registered nurse (ERN) and two paramedics, and the BLS team is composed of two paramedics. Their response is based on clinical practice guidelines according to the pre-established protocols, applying standard life support manoeuvres on the scene or *en route*.

2.2 | Participants

The study included adult patients (aged ≥18 years old) with acute diseases during the study period. Initially, all cases were evaluated and attended by the ALS staff, although later evacuation could be executed either by the ALS or by the

BLS, always at the discretion of the ALS physician. Only patients requiring a venous line due to their clinical situation were selected for this study.

Patients with hospital diagnosis of acute coronary syndrome (according to the Fourth universal definition of myocardial infarction),[13] cases of cardiorespiratory arrest, terminally ill patients (documented with a report from the medical specialist), pregnant women and those situations with risk on the scene were excluded from this study. Patients discharged in situ (after evaluation by the ALS physician) and cases in which no informed consent was obtained were also excluded.

2.3 | Outcome

The primary outcome was in-hospital mortality within 28 days after prehospital attendance, in line with previous studies.[10,14]

The final result of in-hospital mortality was compiled by an associate researcher of each hospital through the review of the patient's electronic medical record.

2.4 | Collection of the parameters and data abstraction

During the first patient care, whether on the scene or en route, the ERN collected data on filiation (age and sex), intervention times (arrival, assistance, evacuation time and time zone), cTnT and type of ambulance that performed the transfer (BLS or ALS).

The prehospital point-of-care cardiac troponin was measured with the POC cobas h 232 analyser (Roche Diagnostics, Mannheim, Germany).[15,16] Before starting the study, all emergency medical service (EMS) members of the ALS team received training to learn the prehospital analysis procedure, including start-up, test performance, cleaning and storage of the test strips. Once the venous line is obtained, a 2.7 mL sample is extracted and placed in a coagulation tube with sodium citrate, model BD Vacutainer® (Becton, Dickinson and Company). After introducing the blood into the tube, it is flipped 3 or 4 times to thoroughly homogenize the sample with the anticoagulant. The prehospital cTnT determination procedure consisted of four phases. 1) The device is turned on and the patient's identification is entered. 2) Insertion of the test strip and waiting for the device to preheat. 3) Apply a 150 μL venous sample of heparinized blood with the Roche cardiac pipette. 4) Wait between 8-12 minutes and the result is obtained on the screen, with a measurement range of 40-2000 ng/L.

To make a link between the EMS medical record and the hospital's electronic medical record, a matching of name and surname, date, age, sex, ambulance code and time of arrival at the ED was accomplished between both records. Five of the six extractors were required to validate the linking of the data.

All patients included in the study were followed for 28 days. After this follow-up period, an associate researcher from each hospital collected the hospital outcomes. In the first place, and depending on the definitive hospital diagnosis, those cases of acute coronary syndrome were excluded. Once this cleaning was done, the following variables were collected: comorbidities, inpatients, need for intensive care unit (ICU) and 28-day in-hospital mortality.

Finally, the diagnosis based on the International Classification of Diseases 11th Revision (ICD-11) was registered, with the following diagnostic groups: infection, neurology, circulatory, respiratory, digestive, trauma and injury, poisoning and other pathology (endocrine, genitourinary and diseases of the blood and the immune system).

2.5 | Statistical analysis

Normality tests were performed on all the quantitative variables (Shapiro-Wilk and Lilliefors tests) resulting in non-normal distributions in all of them; therefore, quantitative variables were described as median and interquartile range (25th-75th percentiles). The categorical variables were described using absolute frequencies with their confidence interval of 95% (95% CI).

For the comparison of means of quantitative variables, the Mann-Whitney U test and the chi-square test were used for 2×2 contingency tables or/and contrast of proportions to stipulate the association or dependency relationship between qualitative variables, and if necessary (percentage of cells with expected values less than five, greater than 20%), the Fisher's exact test was used.

The discrimination capacity of the predictive variable was assessed through a discrimination model by using a generalized linear model. The model included the outcome variable and the discrimination variable cTnT. The discrimination model was built by using a training (two thirds of total patients) and a validation cohort (one third of total patients). Patients were randomly assigned to each cohort by ensuring the same proportion of the outcome for both cohorts. To assess the validity of the model for predicting mortality, we determined the area under the curve (AUC) of the receiver operating characteristic (ROC) of the model in the validation cohort. The P value of the hypothesis test (H0: ABC = 0.5) and its corresponding 95% CI were also assessed. For each putative cofounding variable, the cohort was split in as many categories as the variable has. Then, the aforementioned AUC calculation was performed for each one of the resulting subgroups. Further statistical characteristics as positive

predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and diagnostic accuracy were also calculated.

One of the most valuable characteristics of a predictive model is the capacity of classifying patients according to their mortality risk. We considered thus three categories (high, intermediate and low mortality risk) and by considering the distribution of mortality according to the predictive variable and the detection ranges of the cTnT test, we established cut-off points allowing such patient categorization.

All statistical analyses were performed using our own codes and base functions in R, version 4.0.3 (http://www.R-project.org).

2.6 | Ethics statement

The study was approved by each clinical hospital ethics committee (reference: PI-049-19 and PI-GR-19-1258), registered in the World Health Organization's International Clinical Trials Registry Platform (ICTRP) and available online (doi.org/10.1186/ISRCTN48326533). This study is reported in line with the STROBE statement.

All participants in the study should read and sign the informed consent. During the first visit, the ALS physician was in charge of managing this document. When the patient was conscious with full cognitive capacities, he/she signed the consent by her/himself, which was valid for the duration of the entire study. In the case the patient was not fully conscious, a relative or legal guardian signed the document. In those cases when it was impossible to obtain the consent on the scene or *en route*, the associate researcher of each hospital was in charge of obtaining permission, either with the patient if he was already in a condition to understand and sign the consent, or through contacting a relative or legal guardian. Lastly, in those cases in which an informed consent was impossible to obtain, the case was excluded, and all data related to the study deleted.

3 | RESULTS

The final cohort of this analysis consisted of 848 patients after exclusions (Figure 1). The median age was 68 years (25th-75th percentiles: 50-81 years), and 385 (45.4%) were women. The mortality rate within 28 days was 12.4% (156 cases). The most frequent cause of healthcare demand was circulatory pathologies, followed by neurology, trauma and injury, and infection pathologies. The deaths due to infectious pathologies stand out, which, despite representing 13.3% of total requests for assistance, represent 38.1% of total deaths (40 cases). Deaths of cardiovascular origin were reported in 21% (22 cases); instead, 78% (83 cases) of deaths were of non-cardiovascular cause. In the same way, it was observed that nonsurvivors presented an older age, larger values of cTnT and greater frequency of ICU admissions. Demographic characteristics and clinical data are described in Table 1.

The median cTnT in survivors was 0 ng/L (25th-75th percentiles: 0-46 ng/L) and 71 ng/L (25th-75th percentiles: 51-109) ng/L) in nonsurvivors, without significant differences

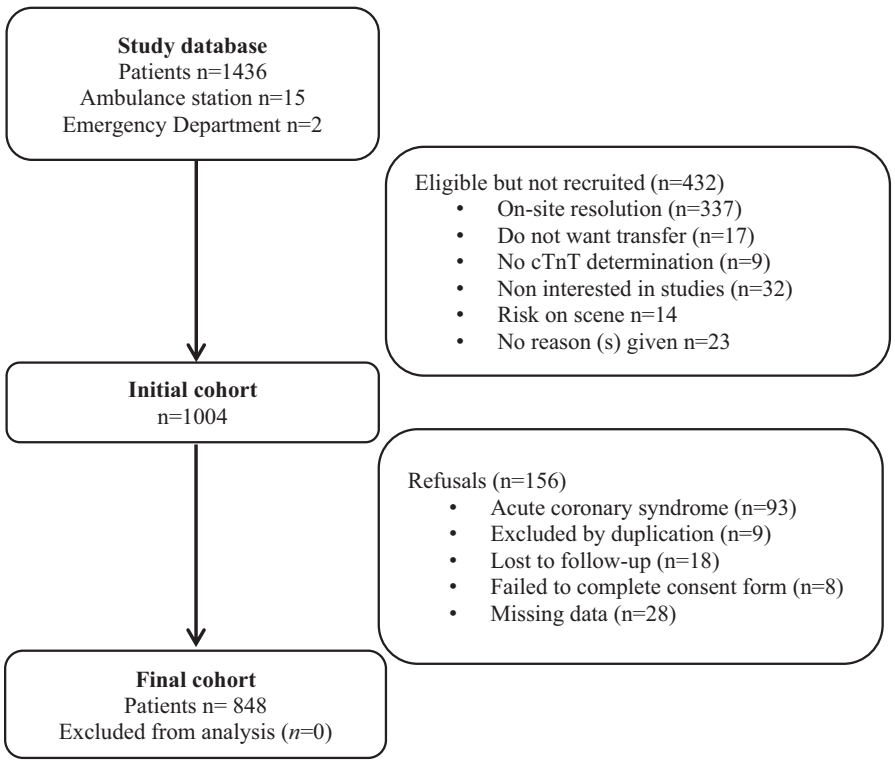

FIGURE 1 Flow chart showing analysis population. cTnT: cardiac troponin

TABLE 1 Baseline patients' characteristics based on in-hospital mortality

	Total cohort[a] (n = 848)	Survivors[a] (n = 743)	Nonsurvivors[a] (n = 105)	*P* value
Sex, female	385 (45.4)	340 (45.8)	60 (57.1)	.576
Age (years)	68 (50-81)	65 (49-78)	81 (69-87)	<.001
Age groups (years)				
18-49	203 (23.9)	196 (26.4)	7 (6.7)	
50-74	321 (37.9)	294 (39.6)	27 (25.7)	<.001
≥75	324 (38.2)	253 (34.1)	71 (67.6)	<.001
Ambulance				
BLS	218 (25.7)	201 (27.1)	17 (16.2)	
ALS	630 (74.3)	542 (72.9)	88 (83.8)	.019
Isochronous (minutes)				
Arrival time	11 (9-15)	11 (9-15)	10 (8-13)	.391
Support time	33 (25-41)	32 (25-40)	37 (29-48)	<.001
Transfer time	10 (8-16)	10 (8-16)	11 (8-15)	.573
Time zone				
06:00-13:59	324 (38.2)	281 (37.8)	43 (41.0)	
14:00-21:59	302 (35.6)	266 (35.8)	36 (34.2)	.590
22:00-5:59	222 (26.2)	196 (26.4)	26 (24.8)	.942
cTnT (ng/L)	0 (0-46)	0 (0-0)	71 (51-109)	<.001
CACI (points)	5 (2-8)	4 (1-7)	9 (7-11)	<.001
Hospital outcomes				
Inpatients	486 (57.3)	381 (51.3)	105 (100)	.992
ICU	156 (18.4)	117 (15.7)	39 (37.1)	
Discharge category				
Circulatory	229 (27.0)	207 (27.9)	22 (21.0)	
Neurology	134 (15.8)	117 (15.7)	17 (16.2)	.567
Trauma and injury	131 (15.4)	122 (16.4)	9 (8.6)	.273
Respiratory	53 (6.3)	45 (6.1)	8 (7.6)	.946
Infection	113 (13.3)	73 (9.8)	40 (38.1)	.194
Poisoning	84 (9.9)	82 (11.0)	2 (1.9)	<.001
Digestive	48 (5.7)	45 (6.1)	3 (2.9)	.194
Others[b]	56 (6.6)	52 (7.0)	4 (3.8)	.856

Note: Abbreviations: ALS, advanced life support; and ICU, intensive care unit; BLS, basic life support; CACI, Charlson age comorbidity index; CI, confidence interval; cTnT, cardiac troponin; OR, odds ratio.

[a]Values expressed as total number (fraction) and medians [25th percentile-75th percentile] as appropriate.

[b]Other pathology: endocrine, genitourinary, diseases of the blood and the immune system.

by sex or diagnostic group, presenting significantly higher cTnT values in older adults and in those with larger number of comorbidities (Table 2). The predictive ability of cTnT to predict 28-day mortality presented an AUC of 0.903 (95% CI: 0.85-0.954; $P < .001$).

Risk stratification was performed resulting in three categories with the following optimal cTnT cut-off points: high risk greater than or equal to 100, intermediate risk 40-100 and low risk less than 40 ng/L. In the high-risk group, the mortality rate was 61.7% (37 cases of 60), with a sensitivity of 84.2%. On the contrary, the low-risk group presented a mortality of 2.3% and a specificity of 97.3% (Table 3). The mortality distribution according to the cTnT risk groups and the predicted probability of mortality is shown in Figure 2.

Finally, in order to rule out the effect of confusion factors on the predictive capacity of the cTnT, the AUC of the ROC for the mortality within 28 days of the cTnT for sex, age and pathology type was assessed. The AUC for females was 0.819 (95% CI: 0.749-0.889; $P < .001$) and for males 0.903 (95% CI: 0.862-0.944; $P < .001$). The younger age range

TABLE 2 Distribution of cTnT in all outcomes analysed

	cTnT (ng/L)			
	Total[a]	**Survivors**[a]	**Nonsurvivors**[a]	***P* value**
Total	0 (0-46)	0 (0-0)	71 (51-109)	<.001
Sex				
Male	0 (0-47)	0 (0-0)	78 (50-113)	
Female	0 (0-45)	0 (0-0)	67 (43-104)	.576
Age groups (years)				
18-49	0 (0-0)	0 (0-0)	200 (76-456)	
50-74	0 (0-20)	0 (0-0)	79 (57-115)	
≥75	20 (0-57)	0 (0-47)	67 (47-104)	<.001
Ambulance				
BLS	0 (0-43)	0 (0-0)	72 (52-104)	
ALS	0 (0-47)	0 (0-0)	71 (50-109)	.017
Hospital outcomes				
Inpatients	0 (0-57)	0 (0-43)	71 (51-109)	<.001
ICU	0 (0-65)	0 (0-47)	67 (42-113)	<.001
Discharge category				
Circulatory	0 (0-59)	0 (0-48)	105 (67-200)	
Neurology	0 (0-0)	0 (0-0)	43 (0-82)	
Trauma and injury	0 (0-0)	0 (0-0)	46 (0-152)	
Respiratory	0 (0-56)	0 (0-48)	62 (42-75)	
Infection	46 (0-79)	0 (0-46)	85 (55-113)	
Poisoning	0 (0-0)	0 (0-0)	60[b]	
Digestive	0 (0-43)	0 (0-0)	53 (49-60)	
Others[c]	0 (0-46)	0 (0-31)	94 (58-159)	.513

Note: Abbreviations: ALS, advanced life support; and ICU, intensive care unit; BLS, basic life support; CACI, Charlson age comorbidity index; cTnT, cardiac troponin.

[a]Values expressed as medians [25th percentile-75th percentile].

[b]25th percentile-75th percentile not calculable (only two cases available).

[c]Other pathology: endocrine, genitourinary, diseases of the blood and the immune system.

(18-49 years) presented an AUC of 0.912 (95% CI: 0.78-0.1; $P < .001$), the middle group (50-74) an AUC of 0.951 (95% CI: 0.926-0.977; $P < .001$) and the older group an AUC of 0.792 (95% CI: 0.73-0.854; $P < .001$). Regarding the pathology type (circulatory, digestive, infection, neurology, poisoning, respiratory, trauma and injury and others), the following AUC was observed: 0.918 (95% CI: 0.877-0.96), 0.933 (95% CI: 0.861-1), 0.863 (95% CI: 0.789-0.936), 0.757 (95% CI: 0.629-0.885), 0.976 (95% CI: 0.942-1), 0.847 (95% CI: 0.733-0.962), 0.742 (95% CI: 0.562-0.922) and 0.952 (95% CI: 0.874-1), respectively (in all cases $P < .001$).

4 | DISCUSSION

In this prospective analysis of patients with acute diseases cared by EMS and transferred with high priority to EDs, prehospital point-of-care cardiac troponin presented an excellent prognostic validity to predict the risk of in-hospital mortality within 28 days.

The use of cTnT is a common practice at the hospital setting,[17,18] standardized in patients with cardiovascular diseases, in particular with acute coronary syndromes.[19-21] In recent years, the development of small and robust point-of-care testing allowed to perform quick and reliable bedside cTnT determinations,[22-24] so there is growing interest in the use of cTnT by EMS to improve the discrimination of patients with chest pain which are potential critical patients on whom is essential to decide the optimal action to be performed and, if necessary, refer the patient to a centre with reperfusion therapy capabilities.[25-27] The use and validity of cTnT in prehospital care to perform triage of patients with chest pain has been proven and its use is now a reality.[11,28,29]

TABLE 3 Statistical details of the global and risk models for cTnT for 28-d mortality

		Risk model cTnT (ng/L)		
	Global	Low [0-40]	Intermediate (40-100]	High (100-779]
Survivors[a]	743 (87.6)	569 (97.7)	151 (73.3)	23 (38.3)
Nonsurvivors[a]	105 (12.4)	13 (2.3)	55 (26.7)	37 (61.7)
Sensitivity[b]	13.7 (12.1-15.3)	2.4 (0-7.3)	40.1 (31.9-48.2)	84.2 (82.8-85.5)
Specificity[b]	97.2 (96.7-97.6)	97.3 (92.4-100)	75.4 (68.4-82.4)	31.3 (29.6-33.1)
PPV[b]	38.3 (37.2-39.4)	0.5 (0-0.6)	49.1 (44.3-53.9)	67.3 (66.9-67.6)
NPV[b]	89.1 (88.8-89.2)	97.7 (97-7-97.7)	78.7 (77.5-80.1)	62.6 (61.5-63.8)
Likelihood ratio (+)[b]	5.02 (4.83-5.21)	0.02 (0-0.07)	NA	NA
Likelihood ratio (−)[b]	0.87 (0.86-0.89)	1 (0.99-1.01)	0.75 (0.69-0.81)	0.42 (0.39-0.43)

Note: Abbreviations: cTnT, cardiac troponin; PPV, positive predictive value; NPV, negative predictive value.

[a]Values expressed as total number (fraction).

[b]Bracketed number indicates 95% confidence interval.

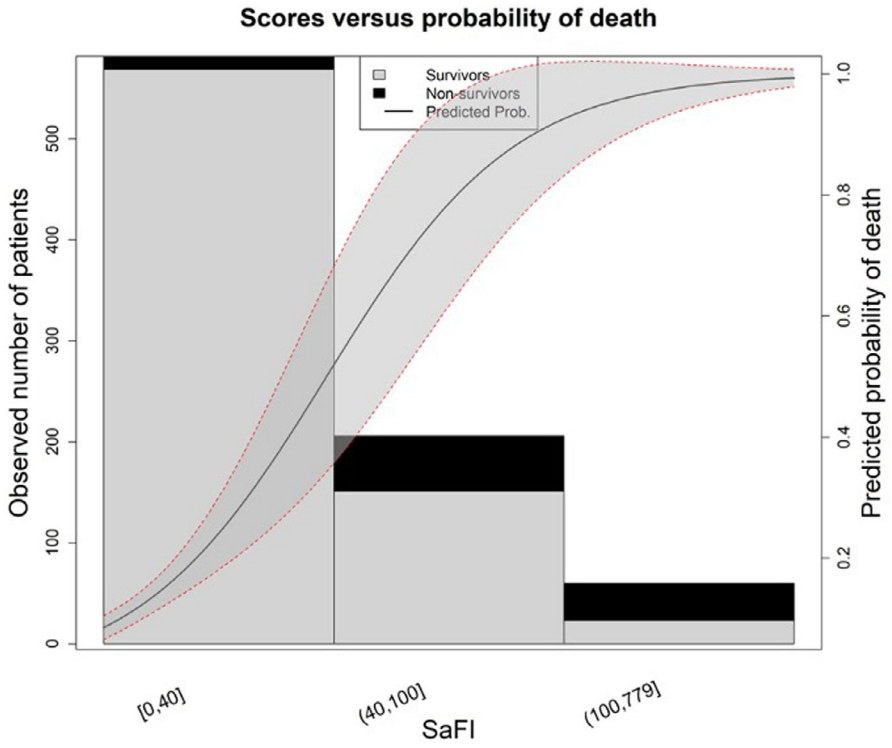

FIGURE 2 cTnT vs. real and predicted probability for 28-d mortality. The grey area of the trend line corresponds to the 95% confidence interval of the predicted probability of death (trend line). The bars correspond to the number of patients of the training cohort alive (grey) or death (black). cTnT, cardiac troponin

An increase in cTnT has been associated with an increase in hospital mortality,[30,31] whereas troponinaemia correlates with an increase in morbidity and the appearance of serious adverse events in both cardiovascular and noncardiovascular diseases.[5,32,33] However, few studies have analysed the influence of prehospital troponin in detecting early mortality in patients without acute coronary syndrome.

Some considerations should be made of the relationship of cTnT with sex, age groups and pathologies. Slightly higher cTnT values were observed in males although without statistical significance.[34] Regarding age groups, there is a direct relationship between elderly and higher mortality, although the highest values of cTnT were obtained among the youngest population cohort (18-49 years) which lowers the threshold of cTnT necessary to increase mortality for older patients. These findings can be explained by the fact that the ability of adapting to acute diseases decreases with age, and moreover, older adults present more comorbidities, both cardiovascular and noncardiovascular.[35,36]

In the analysis of the relationship between cTnT and mortality, in terms of the diagnostic group, higher values of cTnT

were observed in nonsurvivors. Cardiovascular pathologies (excluding the acute coronary syndrome) presented the highest values, but it was the infectious pathology group the one that presented the highest mortality rate.

A risk stratification, an important issue in this context,[37,38] yielded the following results. Levels above 100 ng/L of cTnT indicate high risk with very high mortality rates. This group of patients may require continuous surveillance and more intensive advanced life support manoeuvres. According to our results, the group with cTnT levels below 40 ng/L is a cohort with low mortality in which case the acute demand ischaemia could be ruled out.

4.1 | Clinical relevance

The EMS must assist highly complex patients usually presenting several comorbidities in very different environments, grounding their actions on the sole clinical examination of vital signs and the electrocardiogram. These actions should be made under pressure and as quick as possible having to make decisions with a very high level of uncertainty. This is rather common when syndromic symptoms as chest pain, dyspnoea or syncope appear and deciding the best strategy turns out to be problematic since those symptoms are easily confused with potentially more serious situations.

The use of point-of-care testing is now a reality in prehospital care,[39] and cTnT provides critical information that may help the EMS personnel in the decision-making process, avoiding the underestimation of serious pathologies,[40,41] and acting as an alert trigger for a range of potentially serious pathologies that may help on the best strategy to be followed by these professionals.[42]

4.2 | Limitations

This study has several limitations. First, the data extractors were not blinded. To minimize this bias, the mortality cases were double checked. An associate investigator from each hospital recorded the death within the follow-up period, and subsequently, the principal investigator confirmed the outcome. Second, the sample was recruited by criteria of opportunity. To achieve maximum representativeness, nonstop cases were collected 24 hours a day, every day of the week and continuously, in both rural and urban areas, throughout the study period. Third, the current SARS-CoV-2 pandemic may have directly influenced the data. It can be seen how the death rate from infectious pathology is higher than all other groups of pathologies, but it is the real sample of the real situation experienced. Finally, although it is true that the preliminary global analysis yields robust results, the analysis by pathology groups requires a larger sample.

5 | CONCLUSION

High values of cTnT (troponinaemia) represent a situation of demand ischaemia, in both cardiovascular and noncardiovascular pathologies, a situation that should be evaluated and monitored; this is so due to the fact that a direct association between increased cTnT and the presence of severe diseases is a dangerous situation in which in-hospital mortality increases 28 days from the index event.

The early identification of high-risk patients in the prehospital care is a main goal of the EMS which could certainly improve the management of these patients. In this context, performing bedside cTnT could provide a proven diagnostic and a prognostic aid.

CONFLICT OF INTEREST

None.

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