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High troponin levels and increased risk of serious cardiac complications and death in Puerto Ricans with acute myocardial infarction

Juan Carlos Zevallos[1], Roberto Zevallos[1], Beatriz Collada[1], Roberto Marticorena[1], Reeni Pandya[1], María del Mar Lucio-Paredes[1], Juan Manuel Lozano[1].

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Abstract

Objective: To examine the association of cTnI elevation and risk of serious cardiac complications and in-hospital death in Hispanics with an AMI residing in Puerto Rico. **Material and methods:** Patients from the Puerto Rico Heart Attack Study hospitalized during 2007, 2009, and 2011 with a validated AMI diagnosis and with cTnI obtained within the first 24-hours of admission were included for analysis. cTnI increase ≥10µg/L was defined as high. We utilized logistic regression modeling to examine the association of cTnI levels and serious cardiac complications (atrial/ventricular tachycardia/fibrillation, atrioventricular block, papillary muscle rupture, heart failure and cardiogenic shock) and death while controlling for potential confounders. **Results:** Approximately 52% (1,542) patients met the inclusion criteria. The overall mean age was 66 ± 14 years and 848 (55%) were men. After adjusting for age, gender and comorbidities, patients with high cTnI levels had almost five-times the odds of developing serious cardiac complications (OR=4.8, 95%CI=3.2-7.0; p<0.001) and twice the odds of dying (OR=2.1, 95%CI=1.3-3.3; p=0.002) than those with lower cTnI levels. **Conclusion:** Puerto Ricans with AMI and cTnI levels ≥10µg/L at admission had significantly higher odds of serious cardiac complications and death than those with lower cTnI levels.

Keywords: trombolytic therapy; hispanic; cerebrovascular event

[1]Department of Medical and Population Health Sciences Research, Herbert Wertheim College of Medicine, Florida International University, Miami, Florida, United States

Niveles altos de troponina e incremento de riesgo de complicaciones cardiacas serias y muerte en puertorriqueños con infarto agudo del miocardio

Resumen

Objetivo: Examinar la asociación de niveles de TncI y riesgo de complicaciones cardiacas graves y muerte hospitalaria en puertorriqueños hospitalizados con IAM. **Material y métodos**: Pacientes del Puerto Rico Heart Attack Study hospitalizados durante 2007, 2009 y 2011 con diagnóstico confirmado de IAM y TncI obtenido dentro de las primeras 24-horas de admisión fueron incluidos para el análisis. Niveles de TncI ≥10µg/L fueron definidos como altos. Utilizamos un modelo de regresión logística multivariado para examinar la asociación entre niveles de TncI y complicaciones cardiacas graves (taquicardia/fibrilación atrial/ventricular, bloqueo atrio-ventricular, rotura del músculo papilar, arresto cardíaco, choque cardiogénico) y muerte ajustando por posibles factores de confusión. **Resultados**: Aproximadamente 52% (1,542) de pacientes cumplieron los requisitos de inclusión. El promedio general de edad fue 66±14 años y 848 (55%) fueron hombres. Después de ajustar por edad, género y comorbilidades, pacientes con niveles de TncI altos tuvieron casi cinco veces más riesgo de desarrollar complicaciones cardiacas graves (OR=4.8, 95%CI=3.2-7.0;p<0.001) y dos veces más riesgo de morir (OR=2.1, 95%CI=1.3-3.3; p=0.002) comparado con aquellos con niveles de TncI <10µg/L. **Conclusión**: Puertorriqueños hospitalizados con IAM y niveles de TncI ≥10µg/L durante las primeras 24h de admisión tuvieron riesgo significativamente mayor de presentar complicaciones cardiacas graves y de morir que aquellos con niveles de TncI más bajos en el mismo período.

Palabras clave: terapia trombolítica; hispano; acidente cerebrovascular

Introduction

Acute myocardial infarction (AMI) is the single leading cause of death in the United States and in Puerto Rico. More than 1 million individuals suffer an AMI every year in the United States (1), and approximately one-thousand new cases were registered annually in the Puerto Rico Heart Attack Study (2). Previous studies have demonstrated that abnormal elevation of conventional troponin levels (cTnI), i.e., above threshold values in patients with AMI is an important predictor of mortality and provides important prognostic value (3, 4). In addition, abnormal conventional cTnI levels have been associated with increased electrical complications (auricular and ventricular tachycardia/fibrillation, atrioventricular block), and mechanical complications (ventricular septum, papillary muscle and/or free wall rupture, heart failure (HF), and cardiogenic shock) (5). However, there are contradictory findings, among studies examining the association of the degree of cTnI elevation and the risk of serious cardiac complications and in-hospital mortality (6). In addition, there is a paucity of information on the association of high cTnI levels and complications and dead among Hispanic populations hospitalized with an AMI. The purpose of this study is to evaluate the association of cTnI levels and serious cardiac (electrical and mechanical) complications and in-

Correspondencia a:
Autor Correspondiente: Juan C. Zevallos, MD
Department of Medical and Population Health Sciences Research
Herbert Wertheim College of Medicine
Florida International University
11200 SW 8th Street, University Park, AHC1-338
Miami, FL 33199
Email: juzevall@fiu.edu
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hospital mortality among Hispanic living in Puerto Rico who have been hospitalized with an AMI.

Material and Methods

We reviewed the medical records of Puerto Rican patients hospitalized for possible AMI at 21 academic and/or non-teaching medical, and nonmilitary centers with emergency room capability. According to the United States Bureau Census, the Puerto Rican population is considered mostly Hispanic and in 2010 there were 3,700,000 individuals residing on the Island (7). A complete listing with information on all hospital discharges during study years 2007, 2009, and 2011 with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 410 in the principal and/or secondary diagnosis position, and related acute and chronic coronary disease ICD-9 rubrics (i.e., 412 –old MI, 413 –angina pectoris, 414 – other forms of chronic CHD, and 786.5 –chest pain), was obtained from each of the participating hospitals. Once the computerized discharge diagnosis printouts were obtained from each participating hospital, the appropriate ICD-9-CM codes for CHD were reviewed for purposes of case validation. The list of selected medical records to be reviewed was given to medical record department personnel at each participating hospital. Trained nurse and physician abstractors reviewed the medical records of all identified patients meeting the clinical criteria for AMI developed by the World Health Organization, which includes a clinical history suggestive of AMI, serum enzyme elevations, and serial ECG findings during hospitalization. Since this study was focused on patients with an initial (incident) AMI, records of previous hospitalizations for CHD were reviewed if the hospital chart indicated that the present hospitalization was not the first for CHD. Patients with ECG changes indicative of prior MI (old Q-waves on ECG) or prior documented MI (confirmed by medical records corresponding to prior hospitalizations) were excluded. Patients who developed AMI secondary to an interventional procedure or surgery, other than for the treatment of an acute coronary event, were excluded. Autopsy confirmation of recent onset MI satisfied the study inclusion criteria, irrespective of the other diagnostic criteria. Patients who were initially admitted to the emergency department and stabilized in one hospital, and transferred thereafter to another hospital, were only counted once.

We utilized a standardized data collection form developed in the Worcester Heart Attack Study (8), which was adapted for use in Puerto Rico utilizing a non-concurrent prospective design approach. Study abstractors created an online electronic database with more than 750 variables that included patient's demographic characteristics (i.e., age, gender, municipality of residence); acute presenting symptoms (i.e., chest pressure/discomfort, arm/hand numbness, indigestion/abdominal, back, chest, jaw, left/right arm and shoulder pain, cough, shortness of breath/dyspnea, fever, palpitation/rapid heart rate, sweating/ diaphoresis, vomiting); coronary risk factors and comorbidities (i.e., diabetes, hypertension, hyperlipidemia, smoking, angina, stroke, heart failure); physiologic parameters (i.e., heart rate, blood pressure, lipid profile, serum creatinine or glucose findings); AMI type (i.e., ST-elevation AMI (STEMI) or non-ST-elevation AMI (NSTEMI)); use of invasive coronary procedures (i.e., cardiac catheterization/thrombolysis, percutaneous coronary interventions (PCI), and coronary bypass surgery (CABG)); and hospital survival status. Data were captured electronically utilizing the REDCap™ web application exclusively designed for research studies that allows secure online management of surveys and databases (9).

During the PRHAS years (2007, 2009, and 2011) only conventional (not high-sensitivity) troponin along with CK and CK-MB levels were utilized for AMI biomarker diagnosis in Puerto Rico. In addition, although the decision limit for myocardial injury was established at the 99th percentile of the assay, each

laboratory reported cTnI levels according to their manufacturer's cutoff limits. Because of the potential variations and imprecision in the analytical performance (accuracy and precision) of the troponin assay during this study time span (2007 - 2011), along with the possible utilization of different manufacturers (Abbott, Beckman, Dade, Ortho, and Siemens), platforms (Architect 2000i, Access 2, Dimension Vista, Vitros Eci, and ADVIA Centaur) for cTnI, and their coefficient of variation (CV) at 99th percentile (from 10% - 20%), we sorted the reported values of cTnI (in µg/L) obtained during the first 24 hours of admission and dichotomized in two categories: *high* if the actual cTnI values were at least 10 µg/L, and *low* if the actual cTnI values ranged from above the upper normal limit and below the 10 µg/L.

We defined serious cardiac *electric* complications if any of the following terms were mentioned in the medical record: auricular tachycardia or fibrillation, ventricular tachycardia or fibrillation, and or atrioventricular block. Serious cardiac *mechanical* complications were considered if any of the following terms were mentioned in the medical record: ventricular septum, papillary muscle and/or free wall rupture, heart failure, and cardiogenic shock).

Hypertension, hyperlipidemia, diabetes mellitus and smoking status were included as comorbidities if any of them were ever mentioned in the medical record. In addition, the time since onset of symptoms and time of arrival to the emergency department was defined as "time since symptoms onset".

Only those cases with cTnI levels obtained within the first 24 hours of admission were included in the analysis. Differences in the distribution of continuous variables, such as cTnI levels and age between men and women, were examined by using Student t-test. Chi^2 was utilized to test differences in the proportion of patients having high cTnI levels, e.g., $\geq$10 µg/L and serious electrical and mechanical complications and in-hospital deaths. In addition, initial bivariate logistic regression analysis was utilized to calculate the odds ratios (OR) with 95% confidence intervals of those patients with high cTnI levels and the presence of complications and death during hospitalization. All variables showing statistical significance in association with high cTnI levels, in addition to comorbidities, age and gender were incorporated into a multivariate logistic regression model. For Student t-test and Chi2 analysis, statistical significance was established at the 0.05 level or if the confidence intervals did not overlap. STATA® version 13.0 (10) was used for analysis.

Results

During the study period, conventional cTnI levels were the most common diagnostic biomarker utilized in Puerto Rico. Of the 2,962 patients included in the PRHAS, 52% (1,542) had cTnI levels measured during the first 24 hours of admission. The final study population comprised 848 men (55%) and 694 women with an overall mean age of 66 ± 14 years. The mean cTn I levels was 19.5 ± 2.4 SD µg/L, with men having significantly higher cTnI levels (25.3 ± 1.9 µg/L) than women (19.5 ± 1.4 µg/L), p=0.02. Three out of four patients had a cTnI levels $\geq$ 10 µg/L.

Table 1 shows a breakdown of selected demographics and comorbidities by cTnI level for subjects hospitalized with an AMI. Patients with high CTnI levels were approximately two years older than their counterparts with low cTnI levels (p<0.001). The proportion of men with high cTnI levels was 5% higher than the proportion of men with low cTnI levels (p=0.012). The percentage of hypertensive patients among those with high cTnI levels exceeded by 5.7% the proportion of hypertensive patients in the group with low cTnI levels (p=0.05). Diabetes mellitus was more common among patients with high cTnI values by 3%. The rates of current smoking and complications following hospitalizations were approximately 5% and 3% significantly higher, respectively, among patients with high cTnI levels

compared to those with low cTnI levels. There was no statistically significant difference found in time since symptoms onset, or hyperlipidemia between those with abnormal versus those with low cTnI levels.

Table 1. Distribution of selected demographics and comorbidities by troponin level in Puerto Rican patients hospitalized with acute myocardial infarction in 2007, 2009, 2011 (N=1,542)

Characteristic	cTnI Level		Sig[1]
	≥10 µg/L N (%)	<10 µg/L N (%)	
Age – years, mean (+/- SD)	67.8 (+/-14.0)	65.4 (+/-13.3)	<0.001
Gender (men)	627 (56.8)	221 (51.4)	0.012
Time since symptoms onset – minutes, mean (+/- SD)	614.2 (+/- 583.3)	678.0 (+/- 593.8)	0.277
Hypertension	925 (60.5)	324 (54.8)	0.05
Hyperlipidemia	326 (29.2)	115 (30.2)	0.623
Diabetes mellitus	540 (49.1)	177 (45.8)	0.011
Complications[2]	91 (8.3)	20 (5.2)	0.005
Current smoking	175 (16.1)	43 (11.3)	0.002

[1]Sig. Calculated using Chi square testing for categorical variables and t testing for continuous variables. Significance expressed as p values. Time since symptoms onset, risk factors (hypertension, hyperlipidemia, complications and current smoking status are considered comorbidities.

[2]Complications: Atrial fibrillation, ventricular tachycardia, ventricular fibrillation, shock and/or asystole during hospitalization for acute myocardial infarction.

Table 2 shows the results of bivariate analysis between cTnI levels, age, gender, hypertension, and in-hospital complications and death. Among patients who died during hospitalization, the proportion of those who had high cTnI levels exceeded that of patients with low cTnI levels by 4% (p<0.001). Patients who died were, on average, nine years older than those who survived to discharge (p=0.016). Approximately 2% less men than women died during hospitalization (p=0.014). The proportion of hypertensive patients was 2.6% lower among those who died, as compared to the group of patient who survived. Approximately 22% of patients who died had a documented complication, as compared to the group of patients who survived and experienced no complications during hospitalization (p<0.001). Variables not found to be significantly associated with in-hospital mortality were time since symptoms onset, hyperlipidemia, diabetes, and smoking status.

Table 2. Association between comorbidities and survival status in Puerto Rican patients hospitalized with acute myocardial infarction in 2007, 2009, 2011 (N=1,542)

Characteristic	Survival Status N (%)		Sig[1]
	Dead 180 (11.7)	Alive 1,362 (88.3)	
Troponin (cTnI)			<0.001
High (≥10 µg/L)	131 (7.3)	1,279 (92.7)	
Low (<10 µg/L)	49 (3.2)	83 (96.8)	
Age – years, mean (+/- SD)	75.7 (+/-11.9)	66.5 (+/-13.8)	0.016
Gender			0.014
Men	71 (4.6)	777 (95.4)	
Women	109 (7.1)	585 (92.9)	
Time since symptoms onset – minutes, mean (+/-SD)	843.4 (+/- 587.7)	619.56 (+/- 584.1)	0.394
Hypertension	79 (5.1)	119 (7.7)	0.027
Hyperlipidemia	99 (6.4)	83 (5.4)	0.23
Diabetes mellitus	97 (6.3)	77 (5.0)	0.18
Complications[2]	353 (22.9)	0	<0.001
Current Smoking	74 (4.8)	88 (5.7)	0.53

[1]Sig. Calculated using Chi square testing for categorical variables and t testing for continuous variables, unless otherwise specified. Significance expressed as p values. Time since symptoms onset, risk factors (hypertension, hyperlipidemia, complications and current smoking status are considered comorbidities.

[2]Complications: Atrial fibrillation, ventricular tachycardia, ventricular fibrillation, shock and/or asystole during hospitalization for acute myocardial infarction.

Table 3 depicts a comparison of the unadjusted and adjusted analysis between potential confounders (age, gender, hypertension, and in-hospital complications) and in-hospital mortality. Unadjusted analysis showed that patients with high cTnI levels were 2.4 times more likely to die during hospitalization than patients with low cTnI levels (OR 2.4, 95% CI 1.6-3.7). For every one additional year of age, unadjusted analysis revealed a 10% increase in the odds of in-hospital death (OR 1.1, 95% CI 1.0-1.1). Men had 40% greater odds of dying than women

according to the unadjusted analysis (OR 1.4, 95% CI 1.1-1.9). Patients with hypertension were almost twice as likely to die as compared to patients without hypertension (OR 1.9, 95% CI 1.1-3.6). After adjusting for age, gender, and in-hospital complications, patients with high cTnI levels were still approximately twice as likely to die while hospitalized as patients with low cTnI levels (OR 2.1, 95% CI 1.3-3.3). After adjusting for confounders, a one-year increase in age still resulted in 10% greater odds of in-hospital death (OR 1.1, 95% CI 1.0-1.1). Hypertensive patients held twice the odds of dying (OR 2.0, 95% CI 1.1-3.6). Per the adjusted analysis, those who experienced complications were five times more likely to die during their hospital course than patients without complications (OR 4.8, 95% CI 3.2-7.0). After adjusting for age, gender, hypertension, and in-hospital complications, there was no statistically significant association between gender and in-hospital mortality (OR 1.3, 95% CI 0.95-1.84).

Table 3. Unadjusted and adjusted association between troponin level and in-hospital mortality in Puerto Rican patients hospitalized with acute myocardial infarction in 2007, 2009, 2011 (N=1,542)

Characteristic	Unadjusted OR	95% CI	Sig1	Adjusted OR	95% CI	Sig1
Troponin (high)	2.4	(1.6-3.7)	<0.001	2.1	(1.3-3.3)	0.002
Age (years)	1.1	(1.0-1.1)	<0.001	1.1	(1.0-1.1)	<0.001
Gender (men)	1.4	(1.1-1.9)	0.017	1.3	(1.0-1.8)	0.101
Hypertension	1.9	(1.1-3.6)	0.008	2.0	(1.1-3.6)	<0.001
Complications[2]	5.7	(4.0-8.2)	<0.001	4.8	(3.2-7.0)	<0.001

[1]Sig. Calculated using Chi square testing for categorical variables and t testing for continuous variables. Significance expressed as p values.

[2]Complications: Atrial fibrillation, ventricular tachycardia, ventricular fibrillation, shock and/or asystole during hospitalization for acute myocardial infarction.

Discussion

AMI is diagnosed by increased levels of cardiac biomarkers, together with (a) symptoms, (b) electrocardiographic changes, or (c) imaging findings, consistent with acute myocardial ischemia. Although current guidelines recommend the use of the 99th percentile of a reference population with coefficient of variance ≤10% as a cut-off value for the diagnosis of AMI, until recently, the cTnI assays were insufficiently precise to define reliably the 99th percentile of a normal reference population (11). Further, the current normal reference population levels for troponins are absent for Hispanic populations. The delayed rise in circulating concentrations of cTn after initial symptoms presentation of ischemia was another major limitation of conventional assays. These analytical weaknesses have been successfully overcome by the development of newer assays, the so called high-sensitive troponins.

Findings of this study conducted among Hispanics hospitalized in Puerto Rico are consistent with previous studies that have demonstrated that cTnI above threshold values in patients with AMI is an important predictor of mortality and provides important prognostic value (3,4) In addition, these findings also suggest that there is a statistically significant association between cTnI above threshold values in patients with AMI and increased electrical and mechanical complications, which is consistent with results of the published literature (5).

Conclusion

In summary, Puerto Rican patients with incident AMI who have high cTnI levels in the first 24 hours are twice more likely to progress to serious cardiac complications and in-hospital death. This association persisted despite adjusting for patient age comorbidities. To our knowledge this is the first study to evaluate troponin levels as a predictor of AMI complications and death in Puerto Rico. cTnI levels above (>10µg/L) may detect Puerto Ricans with AMI who may benefit from more intensive monitoring for prevention and early treatment of HF, papillary muscle rupture and death.

Strengths and Limitations

Several researchers have reported a significant association of troponin levels and mortality in the intensive care unit settings (4-6) These findings bring new insight to the prognostic value high levels of cTnI (>10µg/L) in Hispanic patients with incident AMI. In addition, all our cases were independently validated, and our study was performed in 21 different hospitals, which enhance the heterogeneity of the sample. This study has at lease the following limitations: Approximately half of the records did not have cTnI values collected within the 24 hours after admission, and reported in the medical records. The selected ≥10 µg/L cut off point selected to define high cTnI levels, although justified to control for the diverse use of biomarker assay manufacturers and reported cutoff levels at each of the 21 participating laboratories, it is arbitrary. Although we did not specifically validate the electric or mechanical complications mentioned in the medical record with the actual EKG pattern or echocardiogram finding, it would be very unlikely that "cardiac arrest" or "ventricular fibrillation" or "ventricular free-wall rupture" would be mentioned in the medical/nursing notes without having occurred. Finally, finings from this study should be generalized with caution to other populations.

Ethical Aspects

Data for this investigation comes from a de-identified database to protect the subjects from a breach of confidentiality. This study was approved by the Institutional Review Board of all participating hospitals and by the Florida International University. The authors have no conflict of interest to disclose.

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