ORIGINAL ARTICLE

Non-ST Segment Elevation Acute Coronary Syndromes and High-Sensitivity Cardiac Troponin T: Is this the End of the Conservative Strategy?

Síndromes coronarios agudos sin elevación del segmento ST y troponina ultrasensible. ¿Es el final de la estrategia conservadora?

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ABSTRACT

Background: An invasive strategy is recommended in high-risk non-ST segment elevation acute coronary syndromes with elevated high-sensitivity cardiac troponin T levels.
Objectives: The aim of this study was to evaluate in-hospital events in patients undergoing a conservative strategy, analyze the prevalence of elevated high-sensitivity cardiac troponin T levels and its correlation with in-hospital events and establish the predictive value of the biomarker for in-hospital events comparing it with a clinical risk model.
Methods: We conducted an observational and retrospective study. Patients admitted to a coronary care unit with non-ST segment elevation acute coronary syndrome in two centers and treated with a conservative strategy between 2012 and 2017 were included. The clinical risk model was based on the TIMI risk score using the following variables: age > 65 years, two episodes of angina or greater within the past 24 hours, electrocardiographic changes, coronary risk factors, history of coronary artery disease and previous aspirin, excluding high-sensitivity cardiac troponin T levels. The predictive value of high-sensitivity cardiac troponin was compared with the clinical risk model to predict in-hospital events using ROC curves. Combined in-hospital events: recurrent angina, myocardial infarction and mortality. High-sensitivity cardiac troponin T levels > 14 pg/dL were considered elevated.
Results: A total of 245 patients were included. Median age was 65 years (57-76) and 74% were men. Median clinical risk score was 3 (1-4) and 65% of the patients had elevated high-sensitivity cardiac troponin levels. In-hospital events: 55/245 patients (22.4%): recurrent angina, 20,4%; Q-wave myocardial infarction,1.6%; mortality, 0.4%. The prognostic accuracy of high-sensitivity cardiac troponin T to predict in-hospital events was 0.56 (0.48-0.65) compared with the clinical risk model [0.58 (0.49-0.67); p = 0.92] and the TIMI risk score (0.56; p: 0.16).
Conclusions: In patients with non-ST segment elevation acute coronary syndrome, neither high-sensitivity cardiac troponinT levels nor clinical variables were consistent to predict in-hospital events. High-sensitivity cardiac troponin T levels used to guide the therapeutic strategy could lead to an unnecessary indication of procedures with the associated inherent risk.

Key words: Acute Coronary Syndrome – Troponin - Prognosis

RESUMEN

Introducción: Los síndromes coronarios agudos sin elevación del segmento ST con troponina ultrasensible elevada son considerados de alto riesgo por lo que se recomienda una estrategia invasiva.
Objetivos: Evaluar los eventos hospitalarios de los pacientes con tratados con una estrategia conservadora; analizar la prevalencia de troponina ultrasensible positiva y su correlación con eventos hospitalarios; y establecer el valor predictivo de la troponina ultrasensible para eventos hospitalarios y compararla con un modelo de riesgo clínico.
Materiales y métodos: Estudio observacional y retrospectivo. Fueron incluidos pacientes ingresados a una unidad coronaria de 2 centros con síndrome coronario agudo sin elevación del segmento ST, tratados con una estrategia conservadora en el período 2012/2017. El modelo de riesgo clínico utilizado se basó en el Score TIMI con las siguientes variables: edad superior a 65 años, 2 o más dolores en la últimas 24 h, cambios electrocardiográficos, factores de riesgo coronario, antecedentes coronarios y aspirina previa, excluida la troponina ultrasensible. Se comparó mediante curva ROC la precisión pronóstica de la troponina ultrasensible y el puntaje del modelo de riesgo clínico para eventos hospitalarios. Eventos hospitalarios combinados: Angina recurrente, infarto de miocardio y muerte. troponina ultrasensible positiva mayor de 14 pg/dl.
Resultados: Fueron incluidos 245 pacientes. La edad promedio era 65 años (57-76), y el 74% eran hombres. El puntaje del modelo de riesgo clínico fue 3 (1-4) y la troponina ultrasensible positiva se ubicó en el 65%. Eventos hospitalarios: 55/245 pacientes (22,4%): Angina recurrente, 20,4%: infarto tipo, Q 1,6%; muerte, 0,4%. La precisión pronóstica para eventos hospitalarios de la troponina ultrasensible fue 0,56 (0,48-0,65), para el modelo de riesgo clínico 0,58 (0,49-0,67); (p = 0,92) y el Score TIMI 0,56 (p: 0,16).
Conclusiones: En pacientes con síndrome coronario agudo sin elevación del segmento ST ni la troponina ultrasensible ni las variables clínicas al ingreso fueron consistentes para predecir los eventos hospitalarios. Utilizar solo los niveles de troponina ultrasensible para guiar la estrategia terapéutica puede determinar una indicación innecesaria de procedimientos con el consecuente riesgo inherente.

Palabras claves: Síndromes coronarios agudos - troponina - pronóstico

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Abbreviations

NSTE-ACS	Non-ST segment elevation acute coronary syndromes	**CS**	Conservative strategy
hs-cTnT	High-sensitive cardiac troponin T	**CRM**	Clinical risk model
IS	Invasive strategy	**ACS**	Acute coronary syndrome
IHE	In-hospital events	**cTn**	Cardiac troponin

INTRODUCTION

Acute coronary syndromes (ACS) are one of the leading causes of mortality worldwide. In the USA, ACS account for about 780,000 patients hospitalized each year, with three out of four presenting as non-ST segment elevation (NSTE) ACS. (1) Our country lacks a continuous data registry that would let us know the exact incidence of this acute condition, but the proportion of patients hospitalized with each type of acute coronary syndrome is similar. (2) It is important to establish the initial clinical risk of NSTE-ACS, since most of the events (death and myocardial infarction) will occur within the first days of hospitalization. (3) Cardiac troponins (cTn) are currently the biomarkers most commonly used to predict these events. The incorporation of high-sensitive cardiac troponin T (hs-cTnT) assays has required the need for new cut-off values for the diagnosis of myocardial infarction, as most of the studies have been carried out with fourth-generation cTn assays. (4-7) In addition, the guidelines agree that elevated cTnT levels per se also define high clinical risk for in-hospital events (independently of the corresponding TIMI or GRACE risk scores) and thus recommend an early invasive strategy (IS). (8-10) However, this approach is inconsistent with the evidence available, as it failed to demonstrate reduction in in-hospital events (IHE) or 1-year events compared with an early conservative strategy (CS). (11, 12) The aim of this study was to evaluate IHE in NSTE-ACS patients undergoing a CS, analyze the prevalence of positive hs-cTnT levels and its correlation with IHE and establish the predictive value of hs-cTnT levels for IHE comparing it with a clinical risk model.

METHODS

In this observational and retrospective study we included consecutive patients admitted to a coronary care unit with NSTE-ACS in two centers and treated with an early CS between January 2012 and April 2017. NSTEACS was defined by the presence of angina within the past 72 hours associated with at least one of the following: ST-segment depression ≥ 0.05 mV or new T-wave inversion in two or more contiguous ECG leads; increase and decrease of hs-cTnT above the 99th percentile; or history of coronary artery disease: myocardial infarction, myocardial revascularization or coronary angiography with coronary artery stenosis > 70%. Two determinations of hs-cTnT were made within the first 24 h. The clinical risk was calculated using the TIMI risk score. (7, 13) Patients with NSTE-ACS treated with early IE, NSTE-ACS due to secondary ischemia for other conditions, left ventricular dysfunction (EF < 40%), history of myocardial revascularization within the past 6 months and chronic kidney failure were excluded from the study. High-sensitivity cTnT was measured using Roche's Troponin T hs STAT electrochemiluminescent immunoassay. The limit of detection of the assay is 5 ng/L (pg/mL), the 10% coefficient of variation (CV) value is 13 ng/L (pg/mL) and the upper reference limit is 14 ng/L. (14) Any increase or decrease of 20% or greater was considered significant.

The clinical risk model was based on the TIMI risk score, excluding hs-cTnT and using the following variables: age > 65 years, two episodes of angina or greater within the past 24 hours before hospitalization, electrocardiographic changes on admission, coronary risk factors, history of coronary artery disease and previous aspirin. The combination of recurrent angina, myocardial infarction and all-cause mortality was considered as IHE.

Recurrent angina was defined as a new episode of spontaneous angina associated with ischemic changes in the ECG or new elevation of biomarkers (CK ≥ 50% of the baseline level or hs-cTnT > 20%). Myocardial infarction was defined as angina associated with at least two of the following: ST-segment elevation ≥ 0.1mv; CK levels raised to twice the baseline value and new Q waves in two or more contiguous leads at 24 hours. Total mortality was defined as mortality from all causes.

Statistical analysis

Continuous variables were expressed as medians and were compared using the Mann-Whitney test of the Wilcoxon test. Categorical variables were expressed as percentages and were compared using Pearson's chi square test or Fisher's exact test, as applicable. A univariate analysis was performed to establish the predictors of IHE and the results were expressed as odds ratio (OR) with the corresponding 95% confidence interval (95% CI). A p value < 0.05 was considered statistically significant. All calculations were performed using Epi-Info and SPSS statistics 22 packages. A ROC curve was constructed to analyze the area under the curve and define the best sensitivity and specificity of the hs-cTnT value and the clinical risk score with the best accuracy to predict IHE. An area under the curve > 0.70 was considered of good performance. Both ROC curves were compared and the difference between them was considered significant if the p value was < 0.05. The performance of the TIMI risk score was evaluated using a similar method.

Ethical considerations

The study was evaluated and approved by the Ethics Committee and the Scientific Committee of the participating institutions.

RESULTS

Of the 480 patients with NSTE-ACS, 235 were excluded: in 82 patients, the attending physician indicated an invasive strategy, 54 patients had left ventricular dysfunction (EF < 40%), 50 patients had secondary

ischemia associated with chronic kidney failure requiring dialysis (n = 22), sepsis (n = 16) and gastrointestinal bleeding (n = 12), 15 patients due to own decision, 22 patients due to lack of coverage and referral and 12 patients due clinical heart failure. Finally, 245 patients undergoing a CS were analyzed. The main characteristics of the study population are described in Table 1.

Median age was 65 years and 74% were men. Forty-six percent (110/245) of the patients presented ECG changes and 65% had elevated hs-cTnT levels. The TIMI risk score was 3. (2-4) Ninety-six patients (39%) underwent coronary angiography on day 4 (IQR 3-5); 80% of them underwent revascularization (percutaneous coronary intervention in 64.5% and coronary artery bypass graft surgery in 15.5%). The reasons for revascularization were spontaneous angina in 20.4% (50 patients), functional test positive for myocardial ischemia in 17.6% (43 patients) and myocardial infarction in 1.2% (3 patients). The primary outcome occurred in 22.4% of the patients (55/245): recurrent angina in 20.4% (50 patients), Q-wave myocardial infarction in1.6% and all-cause in mortality 0.4% (1 patient). At univariate analysis, ECG changes, positive hs-cTnT and a clinical risk score > 2 were more common in patients with IHE (Table 2).

The ROC curve estimated that the best cutoff point of hs-cTnT to predict IHE was of 14 pg/mL (AUC 0.56: 95% CI, 0.48-0.65; p = 0.14) with a sensitivity of 76% and a specificity of 41%. For the clinical risk model, the best cutoff point was 2 (AUC 0.58: 95% CI, 0.49-0.67; p = 0.06) with a sensitivity of 62% and a specificity of 54%. There were no significant differences between both curves (p = 0.92). For the TIMI risk score, the best cutoff point was 2 (AUC 0.56: 95% CI, 0.48-0.65; p = 0.16) with a sensitivity of 62% and a specificity of 46%. Thus, in our population hs-cTnT alone and the clinical variables gathered in our clinical risk model or their combination included in the TIMI risk score had a poor performance to predict events.

Table 1. Characteristics of the population.

	n: 245 (%)
Age*	65 (53-77)
Men	74
Hypertension	72.7
Dyslipidemia	54
Diabetes	26
Smoking habit	26
History of coronary artery disease	42
ECG changes	46
ST-segment depression	21
Negative T waves	25
hs-cTnT > 14 pg/mL	65
Ejection fraction (EF) >50%	79
TIMI risk score (median)	3 (2-4)
Low risk	68 (28)
Moderate risk	160 (64.5)
High risk	18 (7.5)

*Age, years (median, IQR 25-75%) History of coronary artery disease: includes previous myocardial infarction or myocardial revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). hs-cTnT: High-sensitivity cardiac troponin T. EF: ejection fraction on admission estimated by echocardiography. TIMI risk score: low risk: 0-1; intermediate risk: 2-5; high risk: 6-7. Values are expressed in percentages.

DISCUSSION

Patients with a NSTE-ACS represent a heterogeneous population. Despite they share a common pathophysiology, their demographic, electrocardiographic, serological and clinical variables determine subgroups with different clinical risk. In our population, hs-cTnT alone and the clinical variables gathered in our clinical risk model or their combination included in the TIMI risk score had a poor performance to predict events.

Firstly, the simplistic point of view of basing the outcome on the mere elevation of cardiac troponins in dichotomous fashion has determined an over-indication of procedures that failed to improve the outcome in the short or mid-term and were even detrimental when compared with a conservative strategy. (15-17) In our study, we observed that the elevation of hs-cTnT > 14 pg/mL alone did not demonstrate better prognostic accuracy than the classical clinical variables gathered in our clinical risk model. In fact, in most of our patients the TIMI risk score on admission demonstrated moderate to high risk. Yet, we did not find differences between hs-cTnT and the clinical risk model to predict IHE, with poor performance for both methods. Almost half of our these patients had a history of coronary heart disease and a high prevalence of cardiovascular risk factors, resulting in a high possibility of presenting significant coronary artery disease. Even the performance of the classical TIMI risk score was poor in our patients and with a magnitude that was similar to that of Antman et al. (AUC: 0.63) (12)

In the population included in the GRACE registry, Steg et al. observed that dividing patients into deciles of risk (0-240), the proportion of troponin-positive patients with low or intermediate risk (< 140) and troponin-negative patients, with high clinical risk (≥140) was similar. Hospital death rates for troponin-positive patients ranged from 0% to 15.0% and from 0.1% to 12.7% in troponin-negative patients. (18) Undoubtedly, the abnormalities of the hemodynamic variables included in the design of the score, such as heart rate, blood pressure and Killip class determine high risk subgroups in which the additional value of troponin does not affect the physiological message that reflects ischemic ventricular dysfunction in the same proportion. (19) In studies comparing the results of an early intervention (within 24 h) or delayed intervention (> 36 h after admission), the greatest benefit in reducing

	Without IHE 190 (%)	With IHE 55 (%)	OR (95% CI)	p
Age*	66 (58-75)	61 (53-79)	-	0.50
Hypertension	140 (73.7)	38 (69)	0.80 (0.4-1.5)	0.30
Diabetes	54 (28.4)	10 (18.2)	0.56 (0.3-1.2)	0.08
History of coronary artery disease	78 (41)	24 (43.6)	1.11 (0.6-2)	0.42
ECG changes	56 (29.5)	29 (52.7)	2.67 (1.4-4.9)	0.001
hs-cTnT > 14 pg/mL	116 (61)	42 (76.4)	2.06 (1.0-4.1)	0.02
Clinical risk model > 2	87 (45.8)	34 (61.8)	1.91 (1.03-3.5)	0.02

Table 2. Characteristics of the patients with and without in-hospital events (IHE).
* Expressed in median and interquartile range (25-75%). ECG changes: include ST-segment depression or negative T waves. Clinical risk model > 2: includes all intermediate and high risk patients.

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death/MI/stroke occurred only in the high-risk subgroup (Grace risk score > 140) in which an early invasive strategy was used. (20-22) In addition, even the presence of mild ventricular dysfunction identified a population at higher risk that was probably related to the severity of the stroke or to more diffuse coronary artery disease. (23-24) The incorporation of hs-cTnT has not produced significant improvement in the performance of the GRACE risk score or TIMI risk score to predict all-cause mortality/non-fatal myocardial infarction during hospitalization, at 1 month or at 6 months. (25-28) The evidence that supports the value of troponin alone in defining clinical risk in NSTE-ACS and, thus, the therapeutic strategy, is based on only three studies of poor quality. Yet, these studies are cited by the guidelines as level of evidence to give a recommendation class I. (29-31) In two of these studies, Apple et al. analyzed the predictive value of the change (in percentage) of TnI on admission, 6 h and 24 h. Each study included 370 patients, was not blind and the results were not adjusted for the habitual clinical risk variables. The incidence of mortality, myocardial infarction and requirement of revascularization was greater when the biomarker value increased between 30% and 100% compared with the baseline value. In the third study, Younger et al. (93 patients) observed a good correlation between a single measurement of 72-h troponin I and serial CK measurements in the estimation of myocardial infarct size by magnetic resonance imaging, but they noted that 80% of their patients had ST-segment elevation myocardial infarction on admission.

The TIMI risk score was designed to predict a composite endpoint of mortality, myocardial infarction and recurrent angina requiring revascularization. Thereby, risk factors, a history of coronary artery disease, previous use of aspirin or the number of episodes of angina within the past 72 h play an important role to identify patients at risk for recurrent angina. The prognostic significance of troponin is thus limited.

Finally, in our population adopting a conservative strategy was safe, since angina was the most prevalent event, either spontaneous or induced by a functional test before discharge, with a very low incidence of myocardial infarction and mortality. During hospitalization, an invasive procedure was indicated to those patients with adverse outcome. Thus, the use of a comprehensive strategy improved our performance to dtermine the prognosis.

Study limitations

A selection bias could be possible due to the lack of randomization. One out of three patients was excluded because the attending physician indicated an invasive strategy; this could have contributed to select a population at lower risk. Nevertheless, we believe that patients included with NSTE-ACS represent this condition, as 72% of them had moderate to severe risk according to the TIMI risk score. In addition, 62% of the patients had positive troponin (>14 pg/mL) and according to the current guidelines were high-risk patients and should have undergone coronary angiography. However, only one out of three patients underwent revascularization, particularly due to recurrent angina, with low rate of myocardial infarction and mortality during hospital stay. Of importance, the ICTUS study (32), which randomized high-risk patients based on the presence of positive troponin T on admission, could not demonstrate the long-term benefit of an early invasive strategy compared with an early conservative strategy. With regard to the definition of myocardial infarction as an in-hospital complication, we decided to use the classical definition in order to improve the specificity of the event. We could not categorize our population according to the GRACE score due to the retrospective nature of the study. Nevertheless, this might not have provided additional prognostic information due to the sample size and the low incidence of myocardial infarction/mortality.

CONCLUSIONS

The categorization of the clinical risk of NSTE-ACS on admission using the clinical risk scores is still important. Despite their limitations, the traditional clinical and serological risk factors are tools that allow the evaluation of patients in daily practice admitted

to the coronary care unit and establish risk categories to predict IHE. Cardiac troponin, as the single decision-making tool to determine the outcome and subsequent treatment, is insufficient, as may lead to perform unnecessary interventional procedures with the associated inherent risk. Not even the clinical variables alone or combined are useful to generalize the implementation of a therapeutic approach in a moderate-risk population. During hospitalization, an invasive procedure was indicated to those patients with adverse outcome. Thus, the use of a comprehensive strategy improved our ability to determine the prognosis.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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