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Evaluation of Perioperative High-Sensitive Cardiac Troponin I as a Predictive Biomarker of Major Adverse Cardiovascular Events After Noncardiac Surgery

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ABSTRACT

Background: Various studies suggest that perioperative concentrations of high-sensitivity troponins are incremental and predictive factors of a major adverse cardiac event (MACE) and all-cause mortality. **Objective:** The objective of the study was to evaluate the predictive value of high-sensitivity cardiac troponin I (hs-cTnI) in the development of MACE and all-cause mortality, within 30-days and 1-year follow-up after noncardiac surgery. **Methods:** In this prospective cohort study, we included men ≥ 45 years and women ≥ 55 years with ≥ 2 cardiovascular risk factors and undergoing intermediate or high-risk noncardiac surgery. Demographic and clinical information was collected from clinical charts. We measured baseline hs-cTnI 24 h before surgery, and its post-operative concentration 24 h after surgery. **Results:** In the entire sample, 8 patients (8.6%) developed MACE at 30-days follow-up (4 deaths), 12 (12.9%) within the 1st year (7 deaths), and 17 (18.2%) after complete post-surgical follow-up (10 deaths). We observed higher baseline and post-operative concentrations in patients who presented MACE (12 pg/ml vs. 3.5 pg/ml; p = 0.001 and 18.3 pg/ml vs. 5.45 pg/ml; p = 0.009, respectively). The hazard ratios (HRs) calculated by Cox regression analysis between the hs-cTnI baseline concentration and the post-operative development of MACE at 30-days and 1-year were 5.70 (95% confidence interval [CI], 1.10-29.40) with hs-cTnI > 6.2 pg/ml and 12.86 (95% CI, 1.42-116.34) with hs-cTnI > 3.3 pg/ml, respectively. The estimated post-operative HR death risk at 1-year was 14.43 (95% CI, 1.37-151.61) with hs-cTnI > 4.5 pg/ml. **Conclusions:** Pre-operative hs-cTnI was an independent predictive risk factor for MACE at 30-days and 1-year after noncardiac surgery and for all-cause mortality at 1-year after noncardiac surgery. (REV INVEST CLIN. 2020;72(2):110-8)

Key words: Cardiac troponins. Noncardiac surgery. Major adverse cardiac event. Mortality.

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INTRODUCTION

Cardiac troponins (cTn) are structural proteins of the cardiac myocyte contractile apparatus and the preferred biomarker in the detection of a myocardial lesion[1-3]. According to the Fourth Universal Definition of Myocardial Infarction, the term acute myocardial infarction should be used when cTn values rise and/or fall with at least 1 value above the 99th percentile upper reference limit and at least one of the following: symptoms of myocardial ischemia, new ischemic electrocardiographic changes, development of pathological Q waves, imaging proof of new myocardial injury, or the presence of an intracoronary thrombus by angiography or autopsy[4]. In patients subjected to a surgical procedure, perioperative stress has been reported to precipitate the development of major adverse cardiac events (MACEs)[5]. New high-sensitivity assays can detect very low circulating troponin levels in the general population. These concentrations correlate with the prevalence of associated cardiovascular risk factors, metabolic abnormalities, and/or cardiac dysfunction[6]. The elevation of high-sensitivity troponin in the perioperative period has recently been suggested to be of further prognostic value in the detection of cardiovascular complications[5]. The aim of this study was to evaluate the clinical usefulness of high-sensitivity cTn I (hs-cTnI) in the prediction of MACEs and mortality in patients with established cardiovascular disease or cardiovascular risk factors undergoing noncardiac surgical interventions.

METHODS

We conducted a prospective and longitudinal cohort study in a tertiary care hospital between August 2014 and October 2017. The study was approved by the Institute's Ethics Committee, and a signed clinical consent was obtained from each patient according to the international recommendations in the clinical search.

Patients and hs-cTnI measurements

We identified males ≥ 45 years of age and females ≥ 55 years of age who, according to the stratification of cardiac risk in noncardiac surgical procedures of the American Heart Association (AHA) and the American College of Cardiology (ACC)[7], would undergo intermediate- or high-risk noncardiac surgery. We collected demographic and clinical data from the patients' clinical charts and only included in the study patients who fulfilled at least two of the following cardiovascular risk factors: a history of ischemic heart disease (IHD), cerebral vascular disease (CVD), or heart failure (HF); insulin-dependent diabetes mellitus; dyslipidemia; renal failure with serum creatinine values ≥ 2 mg/dL or in replacement therapy; smoking; and hypertension. All patients with an acute coronary syndrome within 24 h before surgery were excluded from the study. Patients were stratified according to the revised cardiac risk index (RCRI) for pre-operative (PreOp) risk, and the Gupta risk index[8,9].

PreOp hs-cTnI values were determined 24 h before surgery, and a second measurement was obtained 24 h after surgery (PostOp). The ARCHITECT STAT High Sensitive Troponin-I assay was used (B3P253, Abbott Laboratories, Chicago, IL), which has a variation coefficient ≤ 10% in the 99th percentile and measurable concentrations in at least 50% of healthy individuals below the 99th percentile. The upper reference limit, corresponding to the value in the 99th percentile in a healthy reference population, is 26.2 pg/ml according to the assay's insert (15.6 ng/L in females and 34.2 ng/L in males).

Definitions and outcomes

A MACE was defined as the development of an acute coronary syndrome, cardiac arrest, congestive HF requiring hospitalization, percutaneous or surgical coronary revascularization, CVD, peripheral arterial thrombosis, and death due to any cause. The primary outcome was the development of MACE and all-cause mortality within the 1st month. The secondary outcome was considered to be the development of MACE and all-cause mortality after a 1-year follow-up and during the overall follow-up. Follow-up was conducted by telephone and review of the patients' medical charts.

Statistical analysis

We evaluated data normality with the Kolmogorov–Smirnov test. Variables with a normal distribution are expressed as means (m) and standard deviations (SD), while those without a normal distribution are

expressed as medians (med) and interquartile ranges. We compared quantitative variables with a normal distribution with Student's t-test, quantitative variables with a non-normal distribution with Mann–Whitney U-test, and categorical variables with Pearson's Chi-square test (X^2). For the comparison of the pre- and post-levels of hs-cTnI, a t-test for independent samples or Wilcoxon signed-rank test was used according to the distribution. We divided the hs-cTnI measurements into quartiles and compared the events that occurred in each quartile with a X^2 test. We calculated the hazard ratios (HRs) with 95% confidence intervals (CIs) for the development of MACE and mortality at 30 days, 1 year, and throughout overall follow-up. We conducted a multivariate analysis by Cox regression after adjusting for the patients' comorbidities to evaluate the persistence of the detected associations.

ROC curves were created for each outcome to evaluate the test's performance. We established two cutoff points for the different outcomes: the first cutoff point, which was obtained using a multivariate model, represents the PreOp hs-cTnI concentration from which we observed an increased risk of MACE or death; and the second cutoff point, which was obtained according to the highest value of the Youden Index, represents the PreOp hs-cTnI concentration with the best performance. To obtain an internal validation of our study, we carried out a bootstrapping analysis to evaluate the distribution of the difference in probability of MACE for different PreOp hs-cTnI cutoffs. We also calculated the area under the curve (AUC) of the risk indices in the RCRI and Gupta, to compare them with the PreOp hs-cTnI concentration AUC following the method recommended by DeLong et al.[10].

Survival was evaluated by Kaplan–Meier curves and log-rank test. Finally, to evaluate the added predictive ability of the PreOp hs-cTnI to the Gupta risk index, we calculated the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI). All hypothesis tests were two-tailed and $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS Statistics 23 software (IBM Corporation, Armonk, NY), XLSTAT 2017.1 (Addinsoft SARL, New York, NY), and MedCalc Software 18.2.1 (MedCalc, Ostend, Belgium).

RESULTS

We included 93 patients (n = 93) in the study, of which 50 patients (53.7%) were male. The mean age was 67.1 years (SD ± 8.9 years). Median overall follow-up after surgery was 602 days. In the entire sample, 17 patients (18.2%) developed MACE distributed as follows: a total of 8 patients (8.6%) developed MACE at 30-days follow-up, 12 patients (12.9%) during the 1st year, and 17 patients (18.2%) within the overall follow-up. Among patients who developed MACE, we observed 4 deaths in the 1st month, 7 deaths at 1-year follow-up, and 10 deaths in the overall follow-up. No differences were found in sex, age, prevalence of comorbidities, and RCRI between patients with and without MACE, either between alive or dead patients (Table 1).

In the total sample, the hs-cTnI concentration increased postoperatively when compared with the PreOp measurement (3.8 pg/ml vs. 6.3 pg/ml; $p < 0.000$). In patients with MACE, the PreOp and the post-operative concentrations were greater than in those who did not develop MACE (PreOp hs-cTnI: 12 pg/ml vs. 3.5 pg/ml, $p = 0.001$; and PreOp hs-cTnI: 18.3 pg/ml vs. 5.45 pg/ml, $p = 0.009$, respectively; Table 2).

After dividing the PreOp and post-operative concentrations and their difference into quartiles, we observed that in the last quartile of PreOp hs-cTnI (7.06-772.4 pg/ml), a greater incidence of MACE occurred during the overall and 1-year follow-up points when compared with the rest of the inferior quartiles ($p = 0.001$ and $p = 0.006$, respectively). A similar tendency of MACE incidence was observed at the 1st month. As to the PreOp concentration, we only found a greater incidence of MACE in the last quartile (16.71-750.5 pg/ml) during the overall follow-up when compared with the rest of the inferior quartiles ($p = 0.005$). No significant differences were observed in all other comparisons (Fig. 1).

Table 3 shows the PreOp hs-cTnI cutoff points with their respective HRs (95% CI) from which there is an increased risk for the different outcomes obtained by Cox regression analysis (Table S1 shows the bivariate analysis). These association measures were adjusted for age, gender, and the presence of comorbidities,

Table 1. General characteristics of the population

Variables (%)	Total Sample	No MACE group	MACE group	MACE group	MACE group
				Alive	Death
Patients	93 (100)	76 (81.7)	17 (18.3)	7 (41.2)	10 (58.8)
Males	50 (53.76)	41(53.95)	9 (52.5)	3 (42.86)	6 (60.0)
Age in years (±SD)	67.1 (8.9)	67.4 (8.5)	66.7 (10.8)	69.7 (11.0)	64.1 (10.8)
IHD	16 (17.2)	13(17.10)	3 (17.64)	1 (14.28)	2 (20.0)
CHF	13 (13.97)	9(11.84)	4 (23.52)	2 (28.57)	2 (20.0)
Stroke	11 (11.82)	7 (9.21)	4 (23.52)	2 (28.57)	2 (20.0)
HT	65 (69.89)	53 (69.73)	12 (70.58)	5 (71.42)	7 (70.0)
T2DM	27 (29.03)	21 (27.63)	6 (35.29)	4 (57.14)	2 (20.0)
CKD	30 (32.25)	24 (31.57)	6 (35.29)	3 (42.85)	2 (20.0)
Smoking	52 (55.91)	44 (57.89)	8 (47.05)	2 (28.57)	6 (60.0)
Chol >200 mg/dL	14 (15.05)	12 (15.78)	2 (11.76)	1 (14.28)	1 (10.0)
C-HDL <40 mg/dL	31 (33.33)	25 (32.89)	6 (35.29)	2(28.57)	4 (40.0)
Malignancy	39 (41.93)	32 (42.10)	7 (41.17)	1 (14.28)	6 (60.0)
RCRI					
Lee I	41 (44.08)	34(44.73)	7(41.17)	2(28.57)	5(50.0)
Lee II	26 (27.95)	22(28.94)	4(23.52)	2 (28.57)	2 (20.0)
Lee III	18 (19.35)	15(19.73)	3(17.64)	1 (14.28)	2 (20.0)
Lee IV	8 (8.60)	5(6.57)	3(17.64)	2 (28.57)	1 (10.0)

MACE: major adverse cardiac event; SD: standard deviation; IHD: ischemic heart disease; CHF: chronic heart failure; HT: hypertension; T2DM: type 2 diabetes mellitus; CKD: chronic kidney disease; Chol: total cholesterol; C-HDL: high-density lipoprotein cholesterol; RCRI: Revised Cardiac Risk Index.
Categorical variables were compared employing the Pearson's Chi-square test and quantitative variables the Student's t-test.
In all cases, the No MACE Group was compared to the MACE group, as well as the Alive versus Death in the MACE group. No statistically significant differences were observed between groups.

Table 2. Behavior of pre-operative and post-operative hs-cTnI concentration

hs-cTnI	Min-Max (pg/ml)	Med in pg/ml (IQR)	p value
Total sample n=93			
PreOp	0.00–772.40	3.8 (2.3–7.25)	<0.000[×]
PostOp	0.00–750.50	6.3 (3.3–17.1)	
No MACE Group n=76			
PreOp	0.00–52.60	3.5 (2.2–5.97)	[a]<0.000[×]
PostOp	0.00–750.50	5.45 (3.3–10.82)	[b]0.001[†]
			[c]0.009[†]
MACE Group n=17			
PreOp	1.40–772.40	12 (14.15–15.80)	0.094[×]
PostOp	2.10–568.60	18.3 (4.25–90.2)	

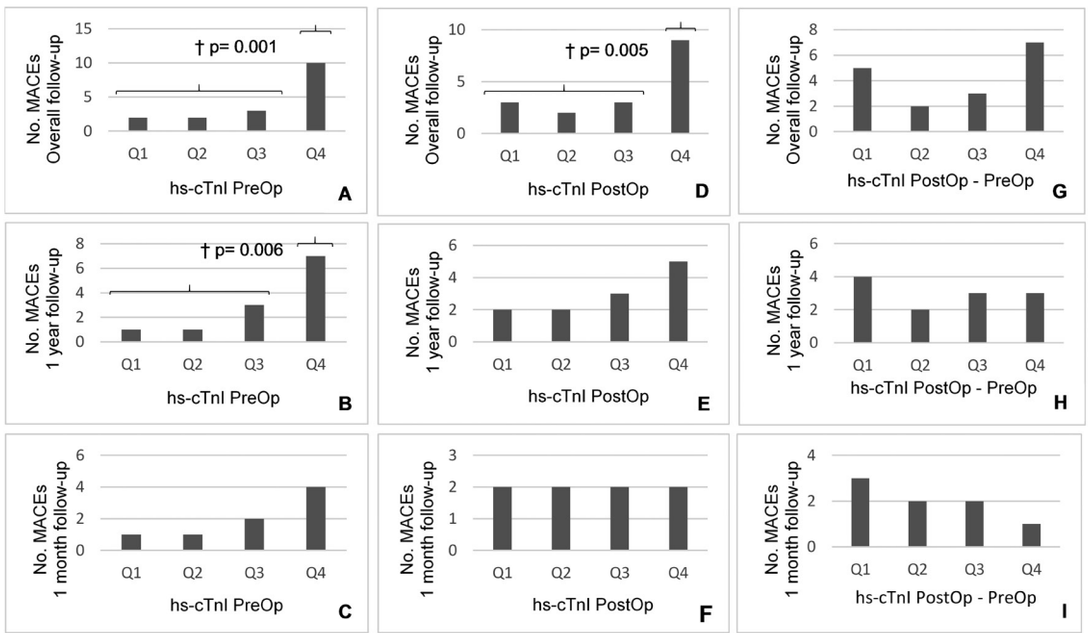
hs-cTnI: high-sensitivity cardiac troponin I; IQR: interquartile range; MACE: major adverse cardiac event; Max: maximum; Med: median; Min: minimum; PostOp: post-operative; PreOp: pre-operative.
[a]Comparison between PreOp and PostOp hs-cTnI in No MACE group. [b]Comparison of PreOp hs-cTnI between No MACE and MACE Groups. [c]Comparison of PostOp hs-cTnI between No MACE and MACE Groups. [×]Wilcoxon signed-rank test. [†]Mann–Whitney U-test.

Table 3. Multivariate analysis (Cox regression) of pre-operative hs-cTnI cutoff points from which an increased risk of MACE or death was observed

PreOp hs-cTnI HR	At 30-days	At 1 year	Overall follow-up
PreOp hs-cTnI (pg/ml)	> 6.2	>3.3	>3.4
HR MACE (95% CI)	5.70 (1.10–29.40)	12.86 (1.42–116.34)	4.13 (1.05–16.13)
PreOp hs-cTnI (pg/ml)	NS	>4.5	>4.2
HR death (95% CI)		14.43 (1.37–151.61)	4.40 (0.83–23.16)

hs-cTnI: high-sensitivity cardiac troponin I; MACE: major adverse cardiac event; PreOp: pre-operative; HR: hazard ratio; CI: confidence interval; NS: nonsignificant.
The multivariate model was adjusted for age, gender, history of ischemic heart disease, chronic heart failure, hypertension, Type 2 diabetes mellitus, chronic kidney disease, Revised Cardiac Risk Index, serum creatinine, and glomerular filtration rate.

Figure 1. Incidence of MACE at 30-days, at 1-year, and throughout overall follow-up, in each pre-operative and post-operative hs-cTnI quartile and changes in each.

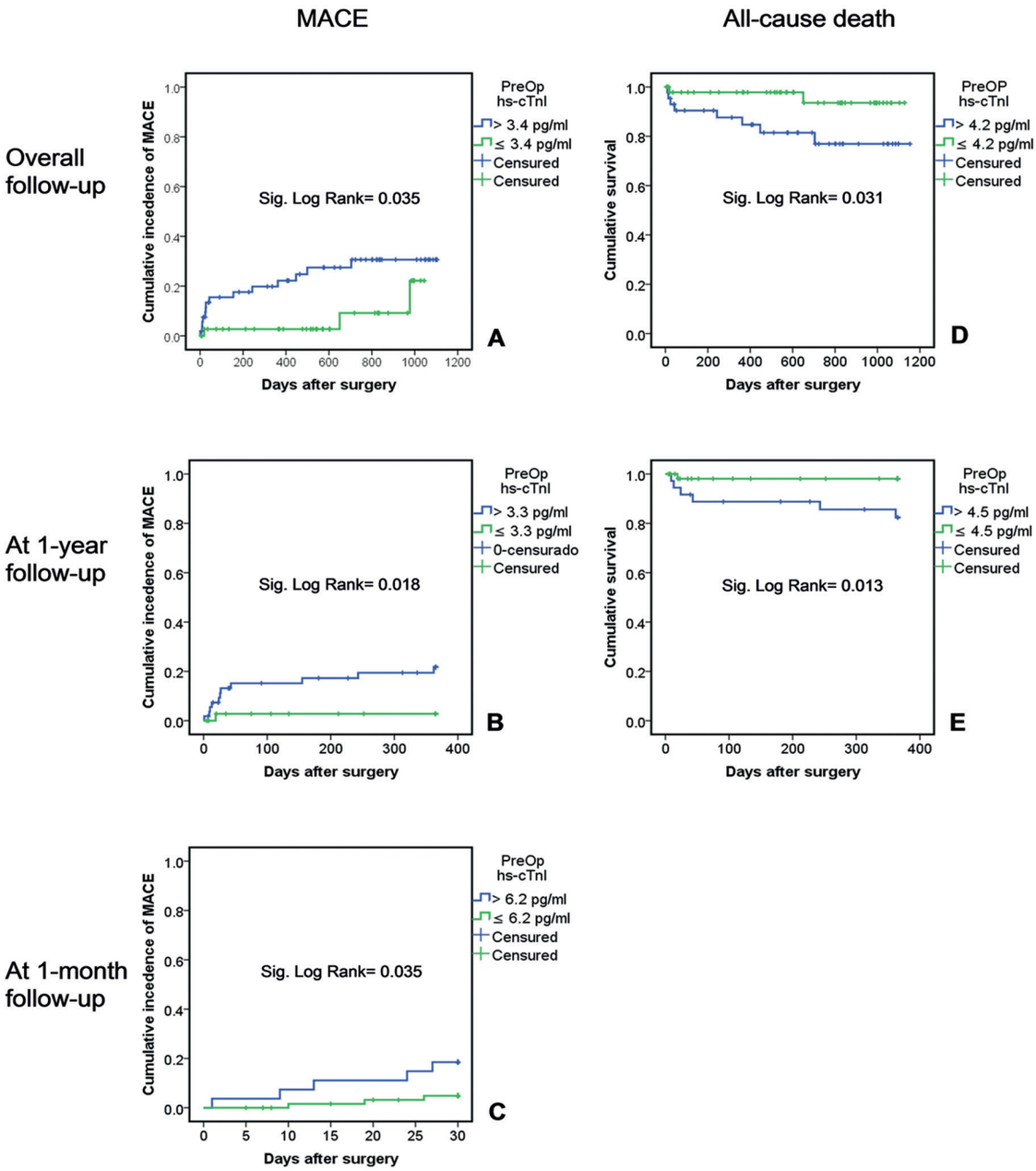


hs-cTnI: high-sensitivity cardiac troponin I, MACEs: major adverse cardiac events, PostOp: post-operative, PreOp: pre-operative, Q: quartile. PreOp hs-cTnI (pg/ml) quartile limits: Q1 (0–2.3), Q2 (2.31–3.8), Q3 (3.81–7.05), Q4 (7.06–772.4). PostOp (pg/ml) quartile limits: Q1 (0–3.3), Q2 (3.31–6.25), Q3 (6.26–16.7), Q4 (16.71–750.5). PostOp limits of the hs-cTnI difference quartiles and PreOp concentration: Q1 (−2103.8–0.1), Q2 (0.11–1.3), Q3 (1.31–6.2), Q4 (6.21–747). †Pearson's Chi-square test (only significant comparisons are shown).

including RCRI. We must emphasize that we did not detect a significantly increased mortality risk at the 30-days follow-up point with the PreOp hs-cTnI concentration in bivariate and multivariate analyses or for mortality at the overall follow-up in multivariate analysis. The bootstrapping analysis shows a normal distribution when analyzing the following cutoff points: 3.3 pg/ml (95% CI, 0.0301-0.3191), 4.5 pg/ml (95% CI, 0.0716-0.4196), and 6.2 pg/ml (95% CI, 0.1229-0.5101; Fig. S1).

In the ROC analysis, we observed a higher PreOp hs-cTnI AUC for MACE and mortality incidence at 1-year and overall follow-up in comparison with the 30-days follow-up AUC. Table S2 shows the measures of accuracy of the identified PreOp hs-cTnI cutoff points. By comparing the AUC of the PreOp hs-cTnI concentration, the Gupta risk index, and the RCRI for the different outcomes, we found greater discriminatory ability of the PreOp hs-cTnI than the RCRI for the incidence of MACE during the overall follow-up (AUC

Figure 2. Kaplan–Meier survival analysis for the development of MACE or death according to the pre-operative hs-cTnI.



hs-cTnI: high-sensitivity cardiac troponin I; MACE: major adverse cardiac event; PreOp: pre-operative.

0.750, [95% CI, 0.649-0.834] vs. AUC 0.546, [95% CI, 0.439-0.650]; p = 0.0387), and also of the Gupta risk index compared with the RCRI (AUC 0.720, [95% CI, 0.616-0.808] vs. AUC 0.546, [95% CI, 0.439-0.650]; p = 0.0387). All other comparisons were not significant (Table S3). Using Kaplan–Meier survival analysis, we found that patients with a PreOp hs-cTnI concentration above the established cutoff points had a greater incidence of MACE and decreased survival (log rank = 0.005) (Figs. 2 and S2).

We determined by NRI analysis ($p < 0.05$) that when using all cutoff points identified in the Cox regression, the PreOp hs-cTnI and Gupta risk index combination

improved the classification of patients with high risk (≥1%) or low risk of developing MACE in comparison with the Gupta risk index (33.55% for MACE at 30-days; 8.70% for MACE and 16.72% for death at 1-year; and 7.70% for MACE and 11.55% for death within the overall follow-up). Furthermore, by IDI analysis we observed an integrated positive difference in Youden's indices with the new model (PreOp hs-cTnI and Gupta risk index combination) in comparison with the Gupta risk index for prediction of MACE at 1-year (IDI 15.56; 95% CI, 3.24-27.88; p = 0.014) and within the overall follow-up (IDI 3.73; 95% CI, 0.92-6.55; p = 0.010) (Table S4).

DISCUSSION

More than 200 million noncardiac surgical procedures are performed in adults every year throughout the world[11], thus increasing the incidence of cardiac death by 0.5%-1.5% and the incidence of MACE by 2% to 3.5%[12]. Since cardiovascular disease remains the main cause of death worldwide[13], the prevention of cardiovascular complications is a current challenge to health systems.

Our findings suggest that elevated PreOp hs-cTnI concentrations in patients with cardiovascular risk factors are independently associated to the development of MACE and death. Borges et al. reported that a peak level of PostOp hs-cTnI > 40 pg/ml was associated to decreased survival and decreased event-free survival by day 30[14]. Likewise, a greater increase in the PreOp and PostOp Δ hs-cTn is associated with a greater incidence of the analyzed outcomes[5,15-18]. Nevertheless, our results show that the PreOp concentration is superior and more clearly associated with the development of MACE in the short and long terms than the post-operative measurement or Δ hs-cTn, with which we detected no relationship whatsoever.

Some studies have found decreased survival and greater incidence of cardiac events when the hs-cTnT PreOp concentration is elevated, using the 99th percentile cutoff point in acute events (14 pg/ml)[15,19,20] or even a greater value (≥17.8 pg/ml)[5]. In our study, PreOp hs-cTnI concentrations remarkably below the 99th percentile represented an increased risk for the evaluated outcomes. Perhaps both troponins (T and I) behave in a similar manner since the VISION study reported that a peak measurement of PostOp hs-cTnT of 5-14 pg/ml increases the risk of death 3.73-fold at 30 days when compared with a concentration < 5 pg/ml (16). Likewise, some studies, as well as some meta-analyses conducted in the general population or the aging population that have not undergone a surgical procedure, have suggested that elevated baseline cTn T or I, below the 99th percentile, is significantly associated with an increased risk of cardiovascular death and all-cause mortality[1,2,6,21-24].

Our study revealed that the risks of MACE and of death begin to increase in accordance with the PreOp hs-cTnI concentration as follows: patients with a value > 6.2 pg/ml have a 5-fold risk of developing MACE in the 1st month after surgery, a concentration > 3.3 pg/ml leads to a 12-fold risk of developing MACE within a year after surgery, and even a value > 4.5 pg/ml leads to a 14-fold increased risk of dying from any cause in the 1st year after surgery. However, the cutoff points with the best performance are as follows: > 6.8 pg/ml for MACE at 1 month, > 7.3 pg/ml for death at 1 month, and > 6.0 pg/ml for MACE, and death during the 1st year. These latter values correlate best with those proposed for the general population (> 6 pg/ml)[6]. We must emphasize that all the mentioned cutoff points have a high negative predictive value (>92%) for all outcomes, similar to the results reported with hs-cTnT[5]; their main use would, therefore, be the identification of patients who, in spite of harboring cardiovascular risk factors, do not require further PreOp evaluation.

The ACC/AHA 2014 perioperative cardiovascular evaluation clinical guidelines recommend that in patients at high risk of developing MACE (≥ 1%) and poor or unknown functional capacity (< 4 METs or metabolic equivalents), a stress test is suggested if it could potentially impact decision making or perioperative care, with the required subsequent approach and management according to the results[25]. Our study suggests that adding a PreOp hs-cTnI measurement to the Gupta risk index improves the classification of patients at low- or high-risk of developing MACE in the short- and long-term post-operative period (30 days and 1 year, respectively) and at low- or high-risk of long-term post-operative death, as well as increases the predictive ability of

MACE in the long-term post-operative period. Further studies with a greater number of patients are necessary to confirm the added value of PreOp hs-cTnI to the Gupta perioperative risk index, as well as to determine the test's impact and cost-effectiveness.

One of our study's strengths is that, to the best of our knowledge, this is the first analysis evaluating the risk of different outcomes with PreOp hs-cTnI concentrations below the 99th percentile; it is also the first to compare the predictive ability of the Gupta risk index when adding the PreOp hs-cTnI value. One of its limitations is the fact that it was conducted in a single center with a small number of patients. Another limitation is that several types of surgeries were included. A strikingly greater proportion of patients with cancer was observed among those who died compared with those who did not, but this difference was not statistically significant (p = 0.059), and the multivariate model was adjusted for malignancy diagnosis. Nevertheless, due to the influence of cancer deaths, it is necessary to consider the results with caution.

In conclusion, patients with cardiovascular risk factors, a PreOp hs-cTnI value above our proposed cutoff points increases the risk of postoperatively developing MACE in the short term and of postoperatively developing MACE or death in the long term. The PreOp hs-cTnI has discrimination similar to the Gupta risk index for the development of MACE and death. However, it seems that the combination of the Gupta risk index and the PreOp hs-cTnI further improve the correct classification of low- or high-risk patients and the predictive ability of MACE.

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SUPPLEMENTARY DATA

Supplementary data are available at Revista de Investigación Clínica online (www.clinicalandtranslationalinvestigation.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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Erratum

In the article by Bello-Chavolla OY and Aguilar-Salinas CA. "Factors Influencing Achievement of Low-Density Lipoprotein Cholesterol Goals in Mexico: The International Cholesterol Management Practice Study", published In Rev Invest Clin. 2019;71(6):408-416, doi: 10.24875/RIC.19003156, it was inadvertently omitted the name of Julieta de la Luz (from Sanofi, Mexico) as second author, on behalf of the Mexico's ICLPS group conformed by César Gonzalo Calvo Vargas (University of Guadalajara, Guadalajara Jal., Mexico) , Edmundo Bayram llamas (Fundación Cardiovascular, Aguascalientes, Ags, Mexico) , Esperanza Martinez Abundis (University of Guadalajara, Guadalajara Jal., Mexico), Gerardo Andres Baez Vargas (private practice, Mexico City, Mexico), Pedro Mendoza Martinez (Hospital Angeles Lindavista, Mexico City, Mexico), Rodrigo Navarrete Valencia (private practice, Mexico City, Mexico) , Bernardo Emilio Valenzuela Salazar (private practice, Chihuahua, Chih., Mexico), Francisco Javier Robledo Gutierrez (private Practice, Mexico City, Mexico), Alfredo Nacoud Askar (Faculty of Medicine, Universidad Autónoma de Nuevo Leon, Monterrey, N.L., Mexico), Carlos Alberto Aguilar Salinas (Instituto Nacional de Ciencias Médicas y Nutrición SZ, Mexico City, Mexico), Sergio Zuñiga Guajardo (Faculty of Medicine, Universidad Autónoma de Nuevo Leon, Monterrey, N.L., Mexico), Maria Elena Cedano Limon (private practice, Mexico City, Mexico), Roberto Bejarano Rodriguez (private practice, Mexico City, Mexico), Lirio de Maria Delgado Garcia (private practice, Chihuahua, Chih., Mexico), Juan Carlos Villanueva Arias (private practice, Guadalajara, Jal. Mexico), Lucia Alejandra Castillo Vigna (private practice, Guadalajara, Jal. Mexico), José Gerardo González González (Faculty of Medicine, Universidad Autónoma de Nuevo Leon, Monterrey, N.L., Mexico), and Martha Leticia López Velazco (private practice, Guadalajara, Jal. Mexico). The authors apologize for this omission.