Perioperative Troponin Screening Identifies Patients at Higher Risk for Major Cardiovascular Events in Noncardiac Surgery

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Abstract: Myocardial injury after noncardiac surgery (MINS) includes patients with traditional myocardial infarction and those with ischemic myocardial injury after surgery. This study evaluated the prognostic value of MINS on major cardiovascular events and 30-day mortality, and determined independent preoperative predictors of MINS in patients after noncardiac surgery. This multicenter prospective cohort study was part of the VISION Study. The sample consisted of 2504 patients who underwent noncardiac surgery at 2 tertiary hospitals in Brazil between September 2008 and July 2012. Troponin Ts were measured 6-12 hours, and on days 1-3 after surgery. Cox regression analyses were performed to identify independent variables of major outcomes. A total of 314 (13%) patients were diagnosed with MINS, of which 26 (8%) died. Length-of-hospital stay of MINS patients was 3 times higher (18 ± 22 days vs 5.8 ± 11 days). In

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multivariate analysis, 30-day mortality was significantly higher among patients with MINS (hazard ratio [HR] 3.17 (95% confidence interval [CI] 1.56-6.41)), and major bleeding (HR 5.76 (95% CI 2.75-12.05)), sepsis (HR 5.08 (95% CI 2.25-11.46)), active cancer (HR 4.22 (95% CI 1.98-8.98)), and general surgery (HR 3.11 (95% CI 1.51-6.41)). Multivariable analysis indicated a higher chance of MINS in patients ≥75 years of age, history of diabetes mellitus, hypertension, heart failure, coronary disease, and end-stage renal failure. The incidence of MINS within 30 days after noncardiac surgery is related to higher mortality. Postoperative troponin monitoring in elder patients and with risk factors for atherosclerotic disease may help reduce postoperative cardiovascular events. (Curr Probl Cardiol 2021;46:100429.)

Introduction

In recent decades, there have been significant advances in surgeries to treat diseases and improve quality of life. As a result, the number of patients undergoing noncardiac surgery is growing, with a worldwide annual estimate of 321 million adults undergoing noncardiac surgery requiring hospitalization.[1] Despite its benefits, noncardiac surgery is associated with major cardiovascular events (ie, vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, and nonfatal stroke)[2] that minimize the expected overall benefits.

A number of studies have shown that elevated serum troponin is an independent predictor of adverse cardiac events and postoperative mortality.[3-5] Its measurement has led to the identification of myocardial injury after noncardiac surgery (MINS) with greater sensitivity and accuracy than the traditional diagnosis of acute myocardial infarction (AMI), since it includes myocardial infarction and asymptomatic myocardial injuries in the first 30 days after noncardiac surgery.[6-8] MINS does not include perioperative myocardial damage of nonischemic etiology (eg, sepsis, pulmonary thromboembolism, and electrical cardioversion).

Despite representing an important public health problem, few studies have provided relevant current information about these outcomes in the middle-low income population.[9-11] Thus, in Brazilian patients undergoing noncardiac surgery, the current incidence of major cardiovascular events

and the usefulness of measuring cardiac markers in the perioperative period remain uncertain.[12,13]

There have been few perioperative cohort studies in Brazilian populations in recent decades, and most have used traditional criteria to determine cardiovascular risk or event evaluation.[14-17] The evaluation of MINS in our population, as well as the identification of risk factors, could contribute to reduced postoperative morbidity and mortality within 30 days after noncardiac surgery.

This study aimed to assess the prognostic value of MINS in relation to major cardiovascular outcomes and 30-day mortality and determine the independent preoperative predictors of MINS in a sample of Brazilian patients after noncardiac surgery. In addition, to evaluate the association between the revised cardiac risk index (RCRI) and MINS as a predictor of major cardiovascular events in this population.

Methods

Study Design and Participants

The VISION study was an international multicenter observational cohort study with prospective data collection. VISION included patients undergoing noncardiac surgery to determine the relationship between troponin T levels in the first 3 days after the procedure and 30-day morbidity and mortality.[6,18] The VISION study recruited 40,004 patients in South and North America, Africa, Asia, Australia, and Europe. Patients were enrolled between August 6, 2007 and July 11, 2012. This substudy includes a sample of all Brazilian patients included in the VISION study. The participating Brazilian Centers were the Hospital de Clinicas de Porto Alegre (HCPA), Porto Alegre, Brazil and the Hospital do Coração (H-COR), São Paulo, Brazil. The VISION Coordinating Center determined that each institution should include between 1000 and 1500 patients in a representative and consecutive sample. At H-COR, enrollment occurred from September 2008 to March 2011, with all surgical patients consecutively included until a total of 1500 was reached. Enrollment occurred at HCPA between August 2011 and July 2012: on 2 days each week that had been randomly predetermined by the VISION Coordinating Center, all surgical patients were included until a total of 1000 was reached.

The VISION study inclusion criteria were patients undergoing elective, urgent, or emergency noncardiac surgery who received general or regional anesthesia (plexus, spinal, or epidural block), aged 45 years or

older, hospitalization for at least 1 night after surgery, and informed consent. The exclusion criteria were patients undergoing surgeries that did not require an overnight stay at the hospital or who received only local or topical anesthesia, patients who withdrew their consent to participate and patients previously enrolled in the VISION Study.

Study Methodology

Patients signed the consent form either before the surgical procedure or within 24 hours after surgery. Patient identification was obtained through preoperative lists posted in preoperative holding areas, surgery rooms or intensive care units. A team of investigators performed the patient interviews, physical examinations, and medical record reviews for potential predictors of major perioperative complications (age, coronary artery disease [CAD], recent high-risk CAD, recent or old myocardial revascularization, cerebrovascular disease, peripheral vascular disease, critical aortic valve stenosis, congestive heart failure [CHF], atrial fibrillation, diabetes mellitus [DM], hypertension [HTN], hypercholesterolemia, history of smoking, and renal impairment). Blood was collected from each patient and tested with either the fourth-generation Troponin T assay (TnT) or the fifth-generation high-sensitivity TnT (hs-TnT), according to availability, between 6 and 12 hours after surgery and on the first, second- and third subsequent days. For patients included between 12 and 24 hours after surgery, laboratory collection was performed immediately upon inclusion and followed the subsequent collections described above. An electrocardiogram (ECG) was performed when troponin levels above the 99th percentile cutoff were detected (TnT $\geq$0.04 ng/mL or hs-TnT $\geq$14 ng/L). If the troponin measurement was elevated, unaccompanied by electrocardiographic changes and unaccompanied by ischemic symptoms or acute pulmonary edema, transthoracic echocardiography was recommended.

Troponin and ECGs results were available to attending physicians to encourage a more detailed and adequate therapeutic approach. During the hospital stay, the researchers conducted evaluations directly with patients and reviewed their medical records, ensuring the periodic collection of troponins and recording clinical outcomes. Both centers reported causes of death (vascular or nonvascular). Thirty days after the procedure, the patients were telephoned to evaluate the outcomes. When evidence of a major clinical outcome was found, the attending physician was contacted and asked to submit the appropriate documentation. The VISION study's data control included data consistency assessment, statistical monitoring,

and local monitoring at all centers. An analysis of the association between troponin and 30-day mortality was planned before data evaluation. The data of patients who could not be followed up for 30 days was considered until the last day their health status was known.

Primary outcome was major vascular events (ie, a composite of vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, CHF, and nonfatal stroke) at 30 days postsurgery.

Secondary outcomes were major bleeding, sepsis, new atrial fibrillation episode, pulmonary embolism, acute renal failure requiring dialysis, and pneumonia. Event definitions were previously published elsewhere.[6]

The VISION Study was registered with clinicaltrials.gov (NCT00512109). To guarantee the participants' safety and minimize their discomfort, follow-up was limited to only procedures strictly necessary for patient monitoring. The confidentiality of patient data was maintained at the local research centers. The study was approved in each Institution Ethics and Research Committee and all patients signed written informed consent before enrollment.

Statistical and Analytical Methods

Categorical variables were described as absolute and relative frequencies, quantitative variables with symmetrical distributions were described with means and standard deviations and asymmetric distributions were described with medians and interquartile ranges. Preoperative baseline characteristics, surgery type, patient comparison regarding mortality and MINS, and stratification according to center (HCOR and HCPA) were reported. To evaluate MINS as an independent predictor of 30-day mortality, the Cox proportional hazard model, adjusted for preoperative and perioperative variables, was used to construct a model of factors independently associated with 30-day MINS. The backward method was used to construct the final model. The results of the models were presented as risk relationships (relative risk [RR] and hazard ratio [HR]) with 95% confidence intervals (CI) and *P* values. To assess the association between the RCRI and MINS, death and MACE, a Poisson regression model was used with robust variance estimates, determining the estimated RRs with 95% CI and *P* values. In all final analyses, *P* values ≤ 0.05 were considered significant. All analyses were performed using SPSS v. 21.

Results

The participants' characteristics are described in Table 1. A total of 2504 patients were included, 1503 from HCOR (São Paulo), and 1001

TABLE 1. Characteristics of the Brazilian population in the 30-day perioperative period

	Total patients N = 2504 (%)	With MINS N = 314 (13%)	Without MINS N = 2190 (87%)	Died 30 d N = 43 (2%)	Survived N = 2461 (98%)
Average age, years (SD)	61.93 (±11)	70.50 (±12)	60.70 (±10)	69.60 (±10)	61.80 (±10)
45-64 y – n (%)	1578 (63)	105 (33)	1473 (67)**	16 (37)	1562 (63)**
65-74 y – n (%)	540 (22)	81 (26)	459 (21)**	14 (33)	526 (22)**
≥75 y – n (%)	386 (15)	128 (41)	258 (12)**	13 (30)	373 (15)**
Female	1287 (51)	137 (43)	1150 (52)*	20 (46)	1267 (51)
Current atrial fibrillation	51 (2)	13 (4)	38 (1)*	2 (4)	49 (2)
History of:					
Diabetes	448 (18)	97 (31)	351 (16)**	14 (32)	434 (17)*
Hypertension	1342 (53)	226 (72)	1116 (51)**	21 (48)	1321 (53)
CHF	106 (4)	40 (12)	66 (3)**	2 (4)	104 (4)
CAD	347 (13)	85 (27)	262 (12)**	4 (9)	343 (13)
High-risk CAD	27 (1)	7 (2)	20 (0.9)*	0 (0)	27 (1)
Late myocardial Revasc.	336 (13)	75 (23)	261 (11)**	5 (11)	331 (13)
Recent myocardial Revasc.	96 (3)	16 (5)	81 (3)*	0 (0)	96 (3)
Peripheral vascular disease	102 (4)	31 (9)	71 (3)**	1 (2)	101 (4)
Stroke	119 (4)	39 (12)	80 (3)**	5 (11)	114 (4)*
COPD	91 (3)	22 (7)	69 (3)*	2 (4)	89 (3)
Active Cancer	423 (16)	82 (26)	341 (15)	23 (62)	396 (16)**
Preoperative medications					
Beta-blockers	427 (12)	90 (28)	337 (15)**	9 (20)	418 (17)
Statins	517 (20)	104 (33)	413 (18)**	9 (20)	508 (20)
Preoperative physical examination					
RC	75 (±12)	76.3 (13)	74.8 (11)*	85.4 (16)	74.8 (11)**
Systolic BP	128.1 (±18)	130.4 (21)	127.8 (17)**	126.5 (26)	128.2 (18)**
Preoperative Glomerular filtration rate					
>60	1450 (58)	116 (37)	1334 (61)	20 (47)	1430 (58)

(*continued on next page*)

TABLE 1. (*continued*)

	Total patients N = 2504 (%)	With MINS N = 314 (13%)	Without MINS N = 2190 (87%)	Died 30 d N = 43 (2%)	Survived N = 2461 (98%)
45-60	198 (8)	51 (16)	147 (7)	6 (14)	192 (8)
30-44	104 (4)*	34 (12)	70 (3)	6 (14)	98 (4)
<30 or dialysis	95 (4)*	55 (17)	40 (2)	7 (16)	88 (3)
without creatinine (*missing*)	657 (26)	58 (18)	599 (27)	4 (9)	653 (27)
Surgery type					
Vascular	107 (4)	32 (10)	75 (3)**	3 (7)	104 (4)
General	459 (18)	77 (24)	382 (17)*	24 (55)	432 (17)**
Thoracic	100 (4)	19 (6)	81 (3)*	2 (4)	98 (4)
Major gynecological/urologic	228 (9)	34 (10)	194 (8)	2 (4)	219 (8)
Major orthopedic	343 (13)	77 (24)	266 (12)**	7 (16)	336 (13)
Major neurological	60 (2)	11 (3)	49 (2)	0 (0)	60 (2)
Low-risk Surgery	1245 (49)	67 (21)	1178 (53)**	5 (11)	1240 (50)**
Type of anesthesia			**		*
General (only or combined)	1764 (70)	250 (79)	1514 (69)	38 (88)	1726 (70)
Spinal/epidural (only)	633 (25)	58 (18)	575 (26)	2 (4)	631 (25)
Local nerve block (only)	98 (3)	6 (1,9)	92 (4)	3 (6)	95 (3)
Other	9 (0.3)	0 (0)	9 (0.4)	0 (0)	9 (3)
Urgent/emergency surgery	66 (2)	19 (6)	47 (2)**	5 (11)	61 (2)*

Data presented as mean and standard deviation for age, heart rate (RC) and systolic blood pressure. ARF, acute renal failure; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral arterial disease; Cockroft-Gault glomerular filtration rate (mL/min).

*$P \leq 0.05$.

**$P \leq 0.001$.

from HCPA (Porto Alegre). The mean age was 61.9 years (SD ± 11), and 51% were female. Within 30 days after surgery, MINS was observed in 314 patients (13%), and 43 patients died (2%). The most common comorbidities were systemic arterial HTN (53%), DM (18%), a history of CAD (13%), myocardial revascularization (13%), and active cancer (16%). The surgeries were mostly low risk (49%), general (18%), or major orthopedic (13%). The most frequent types of anesthesia were general (70%) and spinal or epidural anesthesia (25%).

The baseline characteristics of participants with MINS were mean age of 70.5 years (SD ± 12), female (43%), and history of HTN (72%), DM (31%), CAD (27%), myocardial revascularization (23%), stroke (12%), and active cancer (26%). Patients who underwent general (24%) or major orthopedic surgery (24%) with general anesthesia (79%) had a higher incidence of MINS. The group of patients who died had a mean age of 70 years (SD ± 10), and HTN (48%), DM (32%), history of CAD (9%), and active cancer (62%) were the most frequent comorbidities. Overall length of hospital stay was 7.3 days (SD ± 13.6). The mean length of stays for those with and without MINS were 17.8 days (DP ± 22.9) and 5.8 days (DP ± 10.9), respectively. Baseline participants' characteristics, MINS, and death are presented according to center in Supplemental Table 1A and 1B.

Multivariate analysis of the independent mortality predictors indicated a higher chance of death within 30-day in the group with MINS (adjusted HR 3.17 (95% CI, 1.56-6.41)), major bleeding (adjusted HR 5.76 (95% CI 2.75-12.05)), sepsis (adjusted HR 5.08 (95% CI 2.25-11.46)), and active cancer (adjusted HR 4.22 (95% CI 1.98-8.98)). Regarding surgery type, the chance of death was higher among those undergoing general surgery (adjusted HR 3.11 (95% CI 1.51-6.41)) than any other type (Table 2).

Independent predictors of MINS in the multivariable analysis were age ≥75 years (adjusted HR 2.01 (95% CI 1.54-2.61)), DM (adjusted HR 1.31 (95% CI 1.01-1.69)), HTN (adjusted HR 1.37 (95% CI 1.05-1.79)), CHF and/or CAD (adjusted HR 1.50 (95% CI 1.13-1.98)), and renal insufficiency (preoperative glomerular filtration rate ≤30 mL/min or dialysis (adjusted HR 6.33 (95% CI 4.46-8.99)), whereas female gender (adjusted HR 0.75 (95% CI 0.60-0.95) and low-risk surgery (adjusted HR 0.35 (95% CI 0.27-0.47)) were protective factors (Table 3). Although some patient's characteristics' and surgery types were different between study centers, there was no interaction between centers, MINS and major adverse events.

TABLE 2. Independent variables associated with 30-day mortality after noncardiac surgery

	Patients N = 2504 (%)	Deaths in 30 days N = 43 (2%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Perioperative outcomes				
MINS	314 (13)	26 (8)	11.03(5.98-20.33)**	3.17(1.56-6.41)**
Without MINS	2190 (87)	17 (0.7)	1	1
Major bleeding	167 (7)	23 (13)	17.27(9.48-31.44)**	5.76(2.75-12.05)**
Without major bleeding	2336 (93)	20 (0.8)	1	1
Sepsis	71 (3)	16 (22)	22.30(12.01-41.41)**	5.08(2.25-11.46)**
Without sepsis	2433 (97)	27 (1)	1	1
New atrial fibrillation	12 (0.4)	2 (16)	10.76(2.60-44.49)**	1.34(0.27-6.64)
Without New atrial fibrillation	2492 (99.6)	41 (1)	1	1
Stroke	6 (0.2)	2 (33)	24.17(5.84-100.00)**	2.30(0.37-14.29)
Without stroke	2498 (99.8)	41 (1)	1	1
Pneumonia	34 (2)	6 (17)	12.51(5.28-29.65)**	0.70(0.21-2.30)
Without pneumonia	2470 (98)	37 (1)	1	1
Preoperative variables				
Active cancer	423 (17)	27 (6)	8.45(4.55-15.70)**	4.22(1.98-8.98)**
Without active cancer	2081 (83)	16 (0.7)	1	1
General surgery	459 (18)	24 (5)	5.78(3.16-10.55)**	3.11(1.51-6.41)**
Other surgeries	2045 (82)	19 (0.9)	1	1
Urgent/emergency surgery	66 (3)	5 (7)	0.20(0.07-0.51)**	0.38(0.12-1.11)
Elective surgery	2438 (97)	38 (1)	1	1
History of PAOD	102 (4)	1 (0.9)	0.55(0.07-4.05)	0.35(0.04-2.86)
Without history of PAOD	2402 (96)	42 (1)	1	1
History of DM	448 (18)	14 (32)	2.22(1.17-4.20)*	0.91(0.41-1.99)
Without history of DM	2056 (82)	434 (17)	1	
History of COPD	91 (3)	2 (2)	1.27(0.30-5.25)	1.15(0.26-5.14)
Without history of COPD	2413 (97)	41 (1)	1	1
Age in years:				
45-64	1578 (63)	16 (1)	1	1
65-74	540 (21)	14 (2)	2.55(1.24-5.24)*	1.52(0.68-3.36)
≥75	386 (15)	13 (3)	3.31(1.59-6.89)**	1.69(0.72-3.95)
History of stroke	119 (4)	5 (4)	2.68(1.05-6.81)*	1.57(0.55-4.47)
Without history of stroke	2385 (95)	38 (1)	1	1

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PAOD, peripheral arterial occlusive disease. There was no adjustment for high-risk CAD, DVT, and pulmonary thromboembolism due to zero incidence.

** $P \leq 0.001$.

* $P \leq 0.05$.

Patients with MINS had higher 30-day morbidity, for example, CHF (RR 9.29 (95% CI 3.95-21.89)), MACE (RR 15.55 (95% CI 10.86-22.27)), and mortality (RR 10.66 (95% CI 5.85-19.43)) than those without MINS (Fig).

TABLE 3. Preoperative independent predictors of MINS in the Brazilian population after noncardiac surgery

Patients	Patients N = 2504 (%)	With MINS N = 314 (13%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age ≥ 75 anos	386 (15)	128 (41)	4.40(3.51-5.52)**	2.01 (1.54-2.61)**
Female	1287 (51)	137 (43)	0.71(0.57-0.89)*	0.75 (0.60-0.95)*
History of:				
Current atrial fibrillation	51 (2)	13 (4)	2.29(1.31-4.00)*	1.11(0.61-2.01)
Diabetes	448 (18)	97 (31)	2.21(1.74-2.81)**	1.31 (1.01-1.69)*
CHF	1342 (53)	226 (72)	2.34(1.83-3.00)**	1.37 (1.05-1.79)*
CHF and/or CAD	453 (16)	125 (40)	2.95(2.33-3.74)**	1.50(1.13-1.98)**
COPD	91 (3)	22 (7)	2.20(1.42-3.39)**	1.24(0.77-1.97)
PAD	102 (4)	31 (9)	2.99(2.06-4.34)**	0.84(0.55-1.28)
Stroke	119 (4)	39 (12)	3.00(2.06-4.37)**	1.22(0.85-1.76)
Preoperative glomerular filtration rate				
Without creatinine (missing)	657 (26)	58 (18)	1.10(0.80-1.52)	1.24(0.90-1.71)
<30 or dialysis	95 (4)	55 (17)	11.29(8.18-15.58)**	6.33 (4.46-8.99)**
30-44	104 (4)	51 (16)	4.75(3.24-6.96)**	2.06 (1.34-3.15)**
45-59	198 (8)	34 (12)	3.58(2.57(4.98)**	2.23(1.56-3.18)**
>60	1450 (58)	116 (37)	1	1
Low-risk surgery	1245 (49)	67 (21)	0.25(0.19-0.33)**	0.35 (0.27-0.47)**
Urgent/emergency surgery	66 (2)	19 (6)	2.74(1.72-4.36)**	1.33(0.77-1.97)

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral arterial disease; Cockroft-Gault glomerular filtration rate (mL/min).
** $P \leq 0.001$.
* $P \leq 0.05$.

The correlation between RCRI and cardiovascular outcomes (MINS, MACE, and death) is presented in Table 4. Patients with RCRI II (1 risk factor) were approximately twice as likely to have MINS, 6 times as likely to die and 4 times as likely to have a MACE (HR 2.56 (95% CI 1.92-3.43), HR 6.3 (CI 95% 2.54-15.61), and HR 4.31 (95% CI 2.50-7.43), respectively) than those with RCRI I (no risk factors). The data on intermediate and high-risk RCRI associations, also described in Table 4, reinforce the higher incidence of such events in these subgroups of patients.

When low-risk surgeries were compared to other types, a low incidence (3%) of MINS was observed only among RCRI I (no variable) who underwent low-risk surgery, suggesting that perioperative troponin monitoring in this subgroup is unnecessary. Other results are described in Table 5.

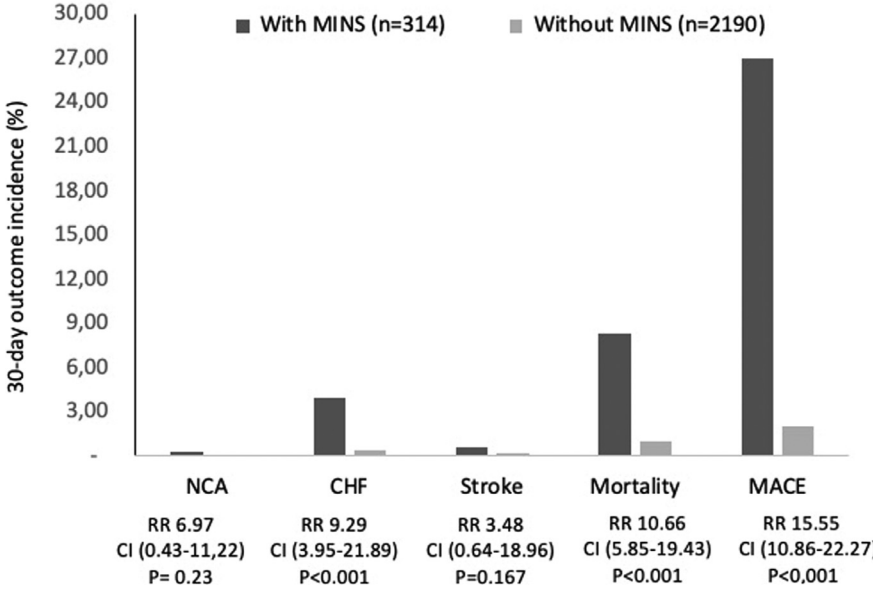

FIG. 30-day outcomes after noncardiac surgery.

CHF, congestive heart failure; MACE, major adverse cardiovascular events: cardiovascular death, nonfatal cardiac arrest, acute myocardial infarction, congestive heart failure and stroke; NCA, nonfatal cardiac arrest.

Discussion

Our study analyzed 2504 Brazilian patients undergoing noncardiac surgery, aged ≥45 years, from 2 tertiary general hospitals. The incidence of MINS was frequent in this population (13%) and correlated significantly with increased mortality and adverse cardiovascular outcomes within 30 days after noncardiac surgery. As predictors of MINS, we identified age ≥75 years, a history of DM, HTN, CHF and/or CAD, and chronic renal failure, whose risk increased with of loss of renal function. Our results were consistent with those of the VISION cohort study published in 2014,[6] in which MINS was an independent predictor of mortality within 30 days after noncardiac surgery (adjusted HR 3.87 (95% CI 2.96-5.08)) and in which MINS was observed in 8% of the patients postoperatively. However, in the VISION study, the correlation between preoperative risk scores was not evaluated.

In the analyses of the association between RCRI and MINS as predictors of events within 30 days after noncardiac surgery showed that low-risk RCRI (1 variable) underestimated the incidence of MACE and death in this population. Kim et al analyzed a cohort of 229 patients undergoing

TABLE 4. Correlation of revised cardiac risk score (RCRI) with cardiovascular outcomes

	MINS N = 314		Death N = 43		MACE N = 58	
RCRI	**N (%)**	**RR (CI)**	**N (%)**	**RR (CI)**	**N (%)**	**RR (CI)**
I (N = 1041)	70 (7)	1	6 (0,6)	1	18 (2)	1
II (N = 550)	95 (17)	2.56(1.92-3.43)**	20 (4)	6.30(2.54-15.61)**	41 (7)	4.31(2.50-7.43)**
III (N = 192)	57 (30)	4.41(3.22-6.04)**	10 (5)	9.03(3.32-24.57)**	29 (15)	8.73(4.95-15.40)**
IV (N = 70)	34 (48)	7.22(5.18-10.05)**	3 (4)	7.43(1.89-29.10)*	20 (28)	16.52(9.16-29.77)**

CI, confidence interval; MACE, major adverse cardiovascular events: cardiovascular death, nonfatal cardiac arrest, acute myocardial infarction, congestive heart failure and stroke; RR, relative risk; RCRI: I (no variables = low surgical risk, risk 0.4%), II (1 variable = low surgical risk, risk 0.9%), III (2 variables = intermediate surgical risk, risk 7%), and IV ($\geq$ 3 variables = high surgical risk, risk 11%).

** $P \leq 0.001$.

* $P \leq 0.05$.

TABLE 5. Incidence of MINS in low-risk patients according to revised cardiac risk score (RCRI)

	Low-risk surgeries N = 1245			Other surgeries N = 1259	
	With MINS N = 67 (5%)	Without MINS N = 1178 (95%)		With MINS N = 247 (20%)	Without MINS N = 1012 (80%)
RCRI I N = 672	N = 17 (3%)	N = 655 (97%)	RCRI I N = 369	N = 53 (14%)	N = 316 (86%)
RCRI II N = 218	N = 32 (15%)	N = 186 (85%)	RCRI II N = 594	N = 154 (26%)	N = 440 (74%)

RCRI: I (no variable = low surgical risk, risk 0.4%), II (1 variable = low surgical risk, risk 0.9%).

vascular surgery and found an association between peak Troponin I (TnI >1.5 ng/mL) 3 days after surgery with increased mortality (RR 5.9 (95% CI 1.6-22.4)) and AMI (RR 27.1 (95% CI 5.2-142.7)) 6 months after surgery.[5] Similar to our results, they also found a significant relationship between elevated troponin and mortality. However, unlike our study, they did not adjust the outcomes for perioperative complications and used a longer follow-up time. Devereaux et al conducted a multivariate analysis of the PeriOperative ISchemic Evaluation study cohort of 8351 patients to evaluate the characteristics of perioperative AMI within 30 days after noncardiac surgery, adjusting both preoperative factors and perioperative complications. This study also demonstrated that the highest quartile of cardiac markers (troponin or creatine kinase-MB ≥3.6 times the upper limit of normality), without ischemic signs or symptoms, was an independent predictor of mortality (adjusted RR 2.54 (95% CI 1.65-3.90)).[19] Published in 2017, the VISION cohort study, consisting of 21,842 postoperative noncardiac surgery patients, found a significant correlation between peak hs-TnT and 30-day mortality. Unlike other studies, the VISION study used the high-sensitivity troponin assay.[7]

To date there is limited evidence on cardiovascular stratification and treatment options for MINS, so that international guidelines have different recommendations regarding perioperative troponin monitoring and guidance on cardiovascular postoperative follow-up and stratification. For instance, Brazilian Guideline on perioperative cardiac risk assessment and management recommends that patients with an intermediate to high estimated perioperative cardiac risk of an ischemic nature should be monitored in semi-intensive or intensive care units with troponin assays and ECGs monitor daily until the third postoperative day (Recommendation Grade I/Evidence Level B).[20] The US Directive[2] considers the usefulness of postoperative troponin screening in patients with a high risk of cardiovascular events to be uncertain in the absence of ischemic signs or symptoms if the cost-benefit of a therapeutic strategy has not been previously established (Recommendation Grade IIb/Evidence Level B) and

contraindicates routine postoperative troponin screening in nonselected patients (Recommendation Grade III/Evidence Level B). The European Guideline[21] recommends monitoring troponin and B-type natriuretic peptide (BNP) in the postoperative period of patients with functional capacity ″4 METS or with RCRI II (1 variable) for vascular surgery and RCRI III (2 variables) for nonvascular surgery (Recommendation Grade IIb/Evidence Level B). Finally, the Canadian Guideline[22] recommends daily troponin monitoring for 48-72 hours after noncardiac surgery in patients with a baseline risk of cardiovascular event >5% (patients with high preoperative BNP or NT-pro-BNP; patients with RCRI II (1 variable); patients aged 45-64 years with a history of cardiovascular disease; patients aged ≥65 years old; Strong Recommendation/Moderate Evidence Level).

Relevant comments in our study include its data from a contemporary representative sample of Brazilian patients undergoing noncardiac surgery, data that are scarce in the literature. All patients had their troponin monitored on the first 3 postoperative days and were prospectively evaluated for ischemic signs and symptoms of TnT ≥0.04 ng/mL or hs-TnT ≥14 ng/L. Our results were consistent with those found in different populations.[6,7,18]

Nevertheless, our study had some limitations. Since troponin was only monitored for 3 days after surgery, the incidence of MINS could have been underestimated due to altered values after this period. Since patients with TnT <0.04 ng/mL or hs-TnT <14 ng/L were not actively screened for ischemic signs and symptoms, the AMI rate may have been underestimated by known infarction criteria. The clinicians who performed the perioperative period follow-up were responsible for attributing nonischemic or ischemic etiology to elevated troponin levels, and some nonischemic etiology may have been underdiagnosed, thus increasing the incidence of MINS.

Although there are few studies testing an effective treatment for patients with MINS, knowing the predictors for such an outcome and its correlation with mortality highlights the need for intensive monitoring and early intervention in these patients. A 2002 meta-analysis of 287 studies that included a total of 135,000 patients demonstrated that antithrombotic therapy with acetylsalicylic acid reduced cardiovascular outcomes in high-risk patients.[23] Statin therapy also plays an important role in preventing primary cardiovascular events, mortality, and major cardiovascular outcomes.[24] In the perioperative setting, a 2014 French study[25] demonstrated that intensified cardiovascular treatment (acetylsalicylic acid, statins, angiotensin-converting enzyme inhibitor, and beta-blockers)

for elevated troponin after vascular surgery was protective for major cardiovascular events compared to controls; as well as data from PeriOperative ISchemic Evaluation trial,[19] The MANAGE study[26] was the first large randomized trial showing that an intermediate dose of dabigatran lowered the risk of major vascular complications compared with placebo in patients with MINS.

These results support the routine monitoring of troponins in at-risk patients after noncardiac surgery because 90% of the participants did not have ischemic symptoms and would have gone unrecognized without troponin monitoring.

Conclusion

MINS incidence within 30 days after noncardiac surgery is significantly related to increased mortality and length of hospital stay. The independent predictors of MINS identified in this study were age ≥75 years, DM, HTN, CHF and/or CAD, and renal failure. Postoperative troponin monitoring can identify cardiovascular outcomes and facilitate early treatment. On the other hand, RCRI I patients who undergo low-risk surgery have a low incidence of MINS, in whom postoperative troponin monitoring may be of no benefit.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2019.05.002.

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