



Perioperative Myocardial Injury After Noncardiac Surgery

Incidence, Mortality, and Characterization

Editorial, see p 1233

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BACKGROUND: Perioperative myocardial injury (PMI) seems to be a contributor to mortality after noncardiac surgery. Because the vast majority of PMIs are asymptomatic, PMI usually is missed in the absence of systematic screening.

METHODS: We performed a prospective diagnostic study enrolling consecutive patients undergoing noncardiac surgery who had a planned postoperative stay of ≥ 24 hours and were considered at increased cardiovascular risk. All patients received a systematic screening using serial measurements of high-sensitivity cardiac troponin T in clinical routine. PMI was defined as an absolute high-sensitivity cardiac troponin T increase of ≥ 14 ng/L from preoperative to postoperative measurements. Furthermore, mortality was compared among patients with PMI not fulfilling additional criteria (ischemic symptoms, new ECG changes, or imaging evidence of loss of viable myocardium) required for the diagnosis of spontaneous acute myocardial infarction versus those that did.

RESULTS: From 2014 to 2015 we included 2018 consecutive patients undergoing 2546 surgeries. Patients had a median age of 74 years and 42% were women. PMI occurred after 397 of 2546 surgeries (16%; 95% confidence interval, 14%–17%) and was accompanied by typical chest pain in 24 of 397 patients (6%) and any ischemic symptoms in 72 of 397 (18%). Crude 30-day mortality was 8.9% (95% confidence interval [CI], 5.7–12.0) in patients with PMI versus 1.5% (95% CI, 0.9–2.0) in patients without PMI ($P < 0.001$). Multivariable regression analysis showed an adjusted hazard ratio of 2.7 (95% CI, 1.5–4.8) for 30-day mortality. The difference was retained at 1 year with mortality rates of 22.5% (95% CI, 17.6–27.4) versus 9.3% (95% CI, 7.9–10.7). Thirty-day mortality was comparable among patients with PMI not fulfilling any other of the additional criteria required for spontaneous acute myocardial infarction (280/397, 71%) versus those with at least 1 additional criterion (10.4%; 95% CI, 6.7–15.7, versus 8.7%; 95% CI, 4.2–16.7; $P = 0.684$).

CONCLUSIONS: PMI is a common complication after noncardiac surgery and, despite early detection during routine clinical screening, is associated with substantial short- and long-term mortality. Mortality seems comparable in patients with PMI not fulfilling any other of the additional criteria required for spontaneous acute myocardial infarction versus those patients who do.

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Clinical Perspective

What Is New?

- In patients with high cardiovascular risk, perioperative myocardial injury (PMI) detected and quantified by an acute increase in high-sensitivity cardiac troponin T plasma concentrations is a common complication after noncardiac surgery occurring in 1 of 7 patients.
- Only 6% of patients with PMI experience typical chest pain, clearly indicating major differences from spontaneous myocardial infarction.
- PMI is associated with substantial 30-day and 1-year mortality (9% and 22%), with similar mortality in patients with PMI not fulfilling the additional criteria for spontaneous myocardial infarction criteria versus those who do.

What Are the Clinical Implications?

- Major differences between PMI and spontaneous myocardial infarction mandate scrutiny in the individualized selection of treatment strategies after PMI.
- The high-risk criteria used in this study (≥ 65 years of age or preexisting atherosclerotic disease) deserve replication in clinical screening programs and research studies aiming at improving 30-day mortality.

Periodic myocardial injury (PMI) has recently been identified as an important, yet often undetected complication after noncardiac surgery, strongly associated with 30-day mortality.¹⁻⁵ In contrast with spontaneous myocardial infarction (MI), PMI most commonly does not exhibit typical symptoms of myocardial ischemia, such as chest pain, angina pectoris, or dyspnea, and is therefore missed in routine clinical practice in most institutions in the United States and worldwide.¹⁻⁵

Considering that >300 million surgeries are performed annually and that demographic change is resulting in an increasing number of surgical patients with elevated cardiovascular risk, strategies to improve the detection, treatment, and outcome of PMI may have the potential to provide major medical benefits. A missed diagnosis inevitably leads to a missed chance for treatment. Therefore, rapid and reliable detection of PMI is a crucial first step in efforts aiming to improve outcomes of this underappreciated perioperative complication. Because ECG also has very low sensitivity,⁶ the detection and quantification of acute cardiomyocyte injury by measuring cardiac troponin (cTn) is critical for the clinical diagnosis of PMI.^{7,8}

Recently, high-sensitivity cardiac troponin (hs-cTn) assays have been introduced into routine clinical care, allowing for the first time the precise detection of acute

cardiomyocyte injury attributable to PMI by using preoperative and postoperative hs-cTn measurements.⁹ The differentiation between PMI and chronic elevations in hs-cTn attributable to chronic cardiac disorders appears paramount for the successful development of strategies to tackle the excess mortality associated with PMI while avoiding overtreatment.

Based on recommendations to screen high-risk patients undergoing noncardiac surgery for PMI,^{7,8} our institution initiated a PMI screening program with a structured response system embedded within clinical routine. The aims of the present study were to (1) assess the incidence of PMI detected by a screening program implemented into clinical routine, which included both pre- and postoperative measurements of high-sensitivity cardiac troponin T (hs-cTnT); (2) evaluate its association with 30-day and 1-year mortality.

METHODS

We adhered to the STROBE reporting guidelines, with further information found in the [online-only Data Supplement](#). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patients

We included consecutive patients undergoing noncardiac surgery at the University Hospital Basel, Switzerland, who were eligible for the institutional routine hs-cTn monitoring program and provided written general consent to registration in a dedicated prospective database. Because the monitoring program was institutional routine, patients did not specifically consent to this standard of care. The study was approved by the local ethics committee (NCT02573532).

Routine screening for PMI was implemented in October 2014 as part of the standard of care for high-risk patients undergoing inpatient noncardiac surgery. Patients were screened if they had a planned hospital stay exceeding 24 hours after surgery and were considered at increased mortality risk, defined as ≥ 65 years of age, or ≥ 45 years with history of coronary artery disease, peripheral artery disease, or stroke. Plasma concentrations of hs-cTnT were measured within 30 days before surgery and on postoperative days 1 and 2, and later if clinically indicated.

Screening was implemented for patients undergoing visceral, orthopedic, trauma, vascular, urologic, spinal, and thoracic surgical procedures. To improve compliance with the screening program, clinicians were alerted automatically of eligibility to the program based on the electronic health records. Serial hs-cTnT measurements were ordered by the treating anesthesiologist. Patients underwent hs-cTnT monitoring and were registered into the database multiple times if a minimum of 5 days had elapsed between procedures.

End Points

PMI was prospectively defined as an absolute increase in hs-cTnT of ≥ 14 ng/L above preoperative values (or between 2

postoperative values if the preoperative value was missing) within 7 days of surgery. Based on findings from prior studies showing that asymptomatic elevations in cTn were also associated with increased short-term mortality,¹ we chose to not mandate specific symptoms or specific ECG changes into the definition of PMI. We used delta values instead of maximum postoperative levels to ensure that our definition reflected acute myocardial damage and was time related to surgery, thus avoiding misclassification of chronically elevated levels. Chronic hs-cTn elevations are expected in a relevant amount of (surgical) patients,¹⁰ and were previously shown to be independently associated with increased risk of death and major adverse cardiac events.¹¹ We chose an absolute rather than a relative delta hs-cTnT level for the diagnosis of PMI, because absolute changes have shown higher diagnostic accuracy than relative changes in the detection of acute myocardial infarction (AMI) in the nonoperative setting.^{12,13} The absolute increase of ≥ 14 ng/L was selected because 14 ng/L represents the 99th percentile of healthy individuals, and, thereby, all PMIs invariably would fulfill the change, and the absolute cTn criteria, as well, required for the diagnosis of spontaneous AMI.⁸

PMI was centrally adjudicated by 2 independent experts based on all clinical information obtained during index hospitalization, including ECG, serial laboratory measurements including hs-cTnT and hemoglobin, monitoring of vital signs in the perioperative and intraoperative period, echocardiography, cardiac stress testing, and coronary angiography, if performed. Two subtypes of PMI were classified: extracardiac in which a primarily extracardiac disease such as severe sepsis, stroke, or pulmonary embolism triggered PMI, and cardiac for all other cases. In cases of disagreement between the 2 reviewers, consensus was sought and found by discussion with a third senior physician.

We further characterized patients as to whether PMI also fulfilled at least one of the additional criteria required for the diagnosis of spontaneous AMI.⁸ Because all PMI necessarily fulfilled the cTn criteria, ≥ 1 of the following was required: the presence of ischemic symptoms, new or presumed new significant ST-segment-T wave changes or new left bundle-branch block, development of pathological Q waves in the ECG, imaging evidence of a new loss of viable myocardium or new regional wall motion abnormality, and identification of an intracoronary thrombus by angiography or autopsy.⁸ The primary event-related prognostic end point was 30-day mortality, and 1-year mortality was the secondary prognostic end point. Deaths were classified as cardiovascular or noncardiovascular according to recent guidelines.¹⁴ Cardiovascular death included death attributable to AMI, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage (eg, ruptured aortic aneurysm or dissection), and pulmonary embolism. All deaths were assumed to be cardiovascular in nature unless evidence of a noncardiovascular cause was available. Noncardiovascular death included all deaths attributable to a clearly documented noncardiac and nonvascular cause, such as respiratory failure (excluding cardiogenic pulmonary edema), infections/sepsis, neoplasm, trauma (including suicide and homicide), and surgical or gastrointestinal bleeding.¹⁴

Procedures

In case of an absolute increase in hs-cTnT of ≥ 14 ng/L above preoperative levels, structured response included assessing patients identified with PMI for possible symptoms related to PMI and recording of a 12-lead ECG by study staff. In addition, a cardiology consultation request was triggered electronically. To address the anticipated problem of insufficient staffing for the substantial number of additional cardiology consultations, particularly during the weekends, it was predefined at the start of the PMI-screening program that, in general, no cardiology consultations attributable to PMI would be performed during the weekends, on public holidays, whenever the cardiologist on call was busy with other, more urgent patients, and in case the patient was currently treated in the intensive care unit (ICU) at the time of PMI detection, because these patients already received intense interdisciplinary care. Nonetheless, hs-cTnT measurements were always available for the treating physician irrespective of the day of the week. All cardiologists providing cardiology consultation after PMI were continuously instructed in a predefined management scheme for PMI (Figure I in the online-only Data Supplement). All treatment decisions regarding PMI were made by the treating surgeon in conjunction with the consulting cardiologist.

We excluded patients who were incorrectly screened (< 45 years, < 24 -hour hospital stay, surgery involving the heart), had their surgery cancelled, had cardiac surgery or MI within 14 days before surgery, if only 1 hs-cTnT concentration was measured, or if postoperative hs-cTnT concentrations were elevated without a dynamic change (≥ 14 ng/L), and preoperative baseline levels were missing. For the analysis addressing 30-day and 1-year mortality, we included every patient only once at first enrollment (Figure II in the online-only Data Supplement).

Data Collection

The Revised Cardiac Risk Index was calculated for all patients.¹⁵ The cardiovascular risk of surgery was classified as proposed by the European Society of Cardiology and the European Society of Anaesthesiology.⁷ During the hospitalization period, we recorded complications (sepsis, stroke, pulmonary embolism, pneumonia, postoperative delirium). Patient symptoms during PMI were extracted from the cardiology consultation report if available, or from electronic health records from the day first exceeding the hs-cTnT-delta threshold of ≥ 14 ng/L. Recommendations given in the cardiology consultations were collected from the electronic health records.

During follow-up, patients were contacted after 1 year by mail or telephone, and local death registries checked. In case of suspicion of an outcome event, study personnel requested reports from the general practitioners, treating facilities, or death registries. Patients lost to follow-up were censored at the last contact with the study team, a hospital, or their general practitioner.

Hs-cTnT Measurements

Hs-cTnT was measured by using an Elecsys System using the Modular Analytics E170 or the Cobas e602 (Roche

Diagnostics) assay with a limit of detection of 5 ng/L, a 10% coefficient of variation at 13 ng/L, and the 99th percentile of a healthy reference population at 14 ng/L.¹⁶ Hs-cTnT was measured within 30 days before surgery, with 83% being measured within 1 day before surgery and 94% being measured within 3 days before surgery.

Statistical Analysis

The incidence of PMI was calculated with 95% confidence intervals (95% CIs) by the method proposed by Agresti and Coull.¹⁷ PMI incidence was stratified by surgical disciplines, European Society of Cardiology/European Society of Anaesthesiology surgical risk,⁷ and postoperative stay on a regular ward or the ICU. The association of PMI with crude all-cause mortality was evaluated by using Kaplan-Meier curves and the log-rank test. To quantify the potential independent effect of preexisting chronic cardiomyocyte injury and acute perioperative cardiomyocyte injury (PMI), we included an analysis that stratified patients into 4 groups according to baseline troponin (low versus elevated) and PMI (acute perioperative elevation present or not). To determine adjusted hazard ratios (HRs), we performed multivariable regression analyses with time to all-cause death as a dependent variable. After evaluation of Schoenfeld residuals, a Cox proportional hazards model was chosen, and the HRs for PMI and its subtypes were calculated adjusted for the predefined covariables age, nonelective surgery, Revised Cardiac Risk Index, and complications during hospital stay (sepsis, stroke, or pneumonia). Based on the number of events and the consensus of requiring 10 events per independent variable compared in regression models, we were able to address 6 variables.¹⁸

Sensitivity Analyses

As reported in the flow chart, missing hs-cTnT measurements prevented definitive PMI adjudication in a subset of patients. We compared the baseline characteristics of these excluded patients with the analyzed cohort (Table I in the online-only Data Supplement).

To evaluate the validity of our outcome analysis, we conducted sensitivity analyses and reran the 30-day mortality model (a) including only cases with complete hs-cTnT measurements preoperative and in the first 2 postoperative days (complete case mode), and (b) censoring all patients if they had a repeat surgery leading to a PMI within 30 days at the time of this later PMI (later PMI censoring).

Hs-cTnT Investigations

To explore the association of absolute hs-cTnT increase and maximum postoperative hs-cTnT level within 7 days of surgery with 30-day mortality, we plotted 30-day mortality according to the increase in and maximum postoperative levels of hs-cTnT using a Loess function using 97.5% of data points.

To evaluate the interaction of preoperative elevations in hs-cTnT ≥ 14 ng/L and PMI, we classified the patients according to PMI status and presence of preoperative hs-cTnT elevation, and constructed Kaplan-Meier curves.

Analysis was done using SPSS 22 and R 3.3 (survminer).

RESULTS

Between October 2014 and November 2015, 2350 patients undergoing 2973 surgeries were screened for PMI. Of these, 2018 patients undergoing 2546 surgeries were eligible for this analysis (Figure II in the online-only Data Supplement).

Incidence of PMI

PMI occurred after 397 of 2546 surgeries (16%; 95% CI, 14%–17%). Patients with PMI had more cardiovascular comorbidities and, consequently, a higher Revised Cardiac Risk Index, and a higher rate of nonelective surgery (Table 1). The incidence of PMI increased with higher European Society of Cardiology/European Society of Anaesthesiology risk category of the surgical procedure from 9% in the lowest to 25% in the highest category (Table II in the online-only Data Supplement).

Table 1. Baseline Characteristics

	All Patients (N=2546)	PMI (n=397)	No PMI (n=2149)	P Value*
Age, y	74 [68–79]	76 [70–81]	73 [68–79]	<0.001
Sex, male	1468 (58)	229 (58)	1239 (58)	0.519
Coronary artery disease	735 (29)	154 (39)	581 (27)	<0.001
Prior myocardial infarction	378 (15)	89 (22)	289 (13)	<0.001
Chronic heart failure	322 (13)	84 (21)	238 (11)	<0.001
Atrial fibrillation	415 (16)	95 (24)	320 (15)	<0.001
Valvular heart disease	306 (12)	72 (18)	234 (11)	<0.001
Peripheral artery disease	475 (19)	106 (27)	369 (17)	<0.001
Prior stroke/TIA	254 (10)	43 (11)	211 (10)	0.295
Hypertension	1694 (67)	292 (74)	1402 (65)	0.001
Diabetes mellitus	621 (24)	129 (32)	492 (23)	<0.001
Lung disease	408 (16)	86 (22)	322 (15)	0.001
Liver disease	166 (7)	30 (8)	136 (6)	0.207
Active tumor disease	674 (26)	84 (21)	590 (27)	0.005
RCRI class				
I	1106 (43)	110 (28)	996 (46)	<0.001
II	814 (32)	130 (33)	684 (32)	
III	419 (16)	91 (23)	328 (15)	
VI	207 (8)	66 (17)	141 (7)	
Elective surgery	1772 (70)	242 (61)	1530 (71)	<0.001
Emergency surgery, ≤ 24 h	314 (12)	69 (17)	245 (11)	
Urgent surgery, >24 h	460 (18)	86 (22)	374 (17)	

Shown for all cases and split for occurrence of perioperative myocardial injuries (PMIs). Data shown as median [interquartile range] or counts (percentage). RCRI indicates revised cardiac risk index; and TIA, transient ischemic attack.

*Comparisons were done using Mann-Whitney *U* or Fisher exact test as appropriate.

PMI incidence differed in patients treated on the surgical ward, patients staying in the ICU for a short period, and patients with prolonged stay (≥ 2 days), with 13% (95% CI, 12–15), 19% (95% CI, 15–23), and 56% (95% CI, 46–65), respectively.

The majority of patients with PMI, 325 of 397 (82%), did not show any ischemic symptoms, and chest pain was only present in 24 of 397 (6%). ECG findings suggestive of myocardial ischemia, especially ST-segment depression or T-wave inversion, were observed in 60 of 244 (24%) of ECGs performed. Together with an additional 7 patients showing evidence of loss of viable myocardium on imaging, overall only 117 of 397 (29%) of patients fulfilled any of the additional criteria required for spontaneous AMI (Table 2).

PMI Subtypes

Three hundred forty-two of 397 PMI (86%; 95% CI; 82–89) were classified as primarily cardiac and 55 of

Table 2. Clinical Presentation, ECG Changes, and Cardiac Workup Within 7 Days in Patients Experiencing a PMI

	PMI (n=397)	Cardiac PMI (n=342)	Noncardiac PMI (n=55)
Ischemic symptoms			
Typical chest pain	24 (6)	19 (6)	5 (9)
Dyspnea	46 (12)	39 (11)	7 (13)
Atypical, but still possible ischemic symptoms	19 (5)	18 (5)	1 (2)
Any ischemic symptoms	72 (18)	59 (17)	13 (24)
Other signs and symptoms			
Palpitations	14 (4)	13 (4)	1 (2)
Edema	39 (10)	35 (10)	4 (7)
Nausea and vomiting	28 (7)	25 (7)	3 (5)
Lung auscultation positive*	38 (10)	27 (8)	11 (22)
(Presumably) new ECG findings [†]			
ST-segment elevation	5 (2)	5 (2)	0 (0)
ST-segment depression	29 (12)	25 (11)	4 (15)
T-wave inversion	27 (11)	25 (11)	2 (8)
New pathological Q waves	1 (0)	1 (0)	0 (0)
Any ischemic ECG changes	60 (24)	54 (25)	6 (23)
PMI fulfilling additional criteria for spontaneous AMI	117 (28)	101 (27)	16 (29)
PMI not fulfilling criteria	280 (71)	241 (70)	39 (71)
PMI fulfilling symptom or ECG change criteria	110 (28)	94 (27)	16 (29)
PMI fulfilling only other additional criteria	7 (2)	7 (2)	0 (0)

Shown also for different PMI subtypes. Data shown as counts (%). AMI indicates acute myocardial infarction; and PMI, perioperative myocardial injury.

*Rales, wheezing, or effusion.

[†]Pre- and postoperative ECG was available in 244 patients.

397 (14%; 95% CI, 10–18) as primarily extracardiac subtypes. The causes for primarily extracardiac PMI were severe sepsis or uncontrolled infection in 40 of 55 patients. The proportion of extracardiac PMI differed between patients treated on the surgical ward (9%; 95% CI, 6–12), patients staying in the ICU for a short period (16%; 95% CI, 9–27), and patients with prolonged ICU stay ≥ 2 days (38%; 95% CI, 26–51).

Mortality Associated With PMI

Among 2018 patients eligible for analysis, 30-day follow-up was complete in 99.9%, and 1-year follow-up was complete in 99.6% of patients. Overall, 56 of 2018 patients (2.8%; 95% CI, 2.1–3.6) died within 30 days; 23 (41%; 95% CI, 29–54) died of cardiovascular causes and 33 (59%; 95% CI, 46–71) died of noncardiovascular causes. One year after surgery, 224 of 2018 (11.2%; 95% CI, 9.8–12.7) patients died; 71 (32%; 95% CI, 26–38) died of cardiovascular causes and 153 (68%; 95% CI, 62–74) died of noncardiovascular causes. Data on the surgical course and hospital stay can be seen in Table III in the online-only Data Supplement, and the number of cardiology consultations, cardiac imaging, and changes in cardiovascular medication can be seen in Table IV in the online-only Data Supplement.

At 30 days, 28 of 285 (9.8%; 95% CI, 6.8–14.0) patients with PMI versus 28 of 1733 (1.6%; 95% CI, 1.1–2.4; $P < 0.001$) patients without PMI had died (Figure 1A). Cardiovascular death occurred in 14 of 285 (4.9%; 95% CI, 2.8–8.2) patients with PMI in comparison with 9 of 1733 (0.5%; 95% CI, 0.3–1.0) patients without PMI.

At 1 year, 64 of 285 (22.5%; 95% CI, 17.9–27.8) patients with PMI versus 160 of 1733 (9.3%; 95% CI, 8.0–10.8; $P < 0.001$) patients without PMI had died (Figure 1B). Cardiovascular death occurred in 26 of 285 (9.1%; 95% CI, 6.2–13.2) patients with PMI in comparison with 45 of 1733 (2.6%; 95% CI, 1.9–3.5) patients without PMI.

In multivariate regression analysis, PMI was associated with a HR of 2.7 (95% CI, 1.5–4.8; $P = 0.001$) for 30-day mortality, and a HR of 1.6 (95% CI, 1.2–2.2; $P = 0.003$) for 1-year mortality (Table 3).

Patients with PMI not fulfilling additional criteria required for spontaneous AMI had comparable 30-day mortality and 1-year mortality rates to patients with PMI fulfilling ≥ 1 of the additional criteria required for spontaneous AMI (10.4% [95% CI, 6.7–15.7] versus 8.7% [95% CI, 4.2–16.7]; $P = 0.684$ and 22.1% [95% CI, 17.6–27.5] versus 29.1% [95% CI, 21.4–38.1]; $P = 0.47$; Figure 2). When analyzing different PMI subtypes, 30-day mortality was 15 of 245 (6.1%; 95% CI, 3.6–10.0) versus 13 of 40 (32.5%; 95% CI, 19.8–48.4; $P < 0.001$, Figure 1C and 1D) in patients with PMI of car-

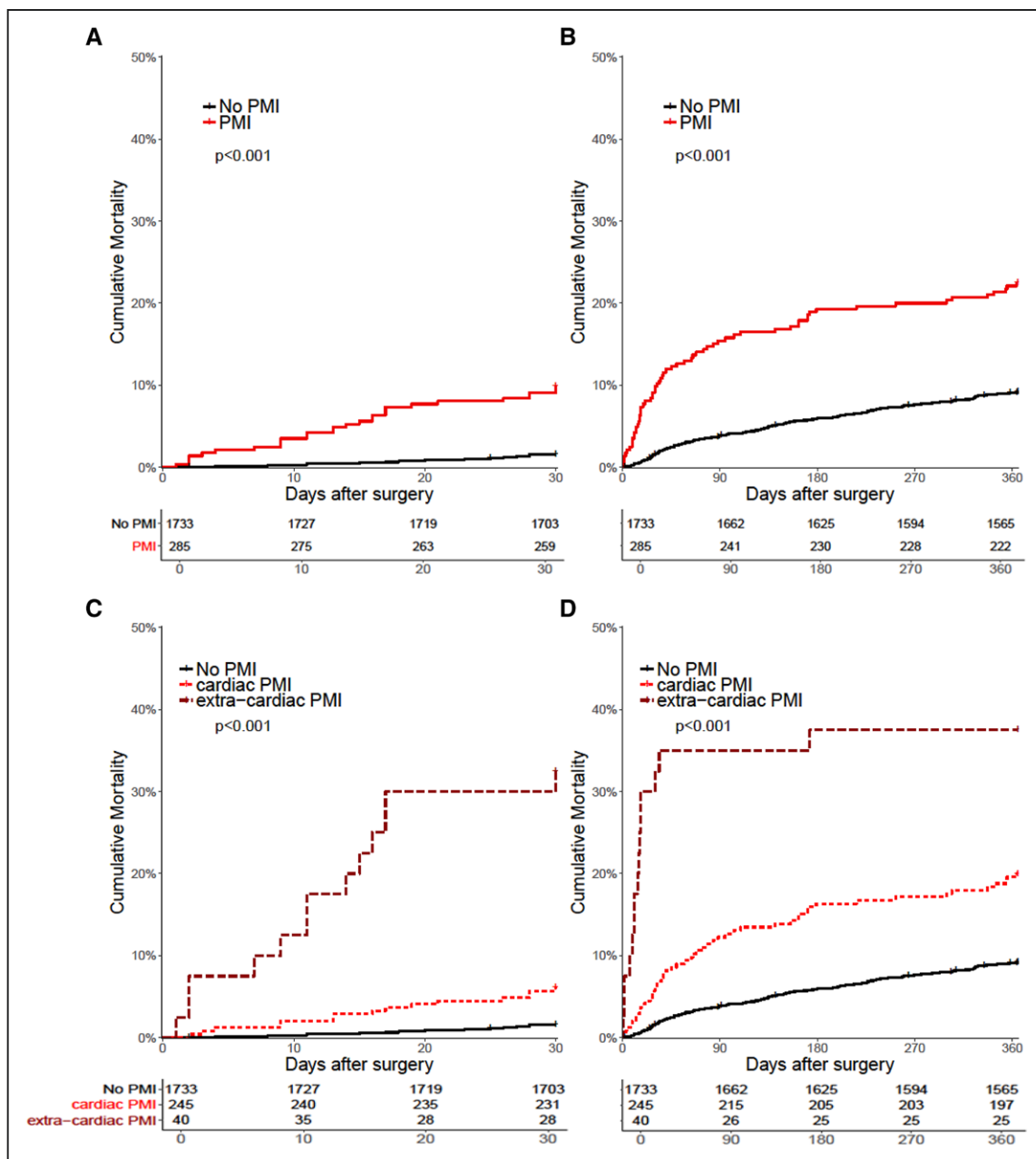


Figure 1. Mortality of perioperative myocardial injury.

Cumulative all-cause mortality within 30 days and 1 year, shown for patients with (red) and without (black) perioperative myocardial injury (PMI) (A and B), and patients according to PMI subtypes: cardiac PMI (dotted line), PMI associated with primarily noncardiac disease, such as severe sepsis (extracardiac PMI, dashed line), and patients without PMI (solid line) (C and D).

diac and extracardiac subtype, respectively. In the group of patients with cardiac PMI, 60% of deaths within 30 days of surgery were cardiovascular, in comparison with 39% in patients with extracardiac subtype.

At 1 year, 49 of 245 (20%; 95% CI, 15–26) patients with a cardiac PMI versus 15 of 40 (38%; 95% CI, 24–53) patients with an extracardiac PMI had died. In the group of patients with cardiac PMI, 43% of deaths within 1 year of surgery were cardiovascular, in comparison with 33% in patients with extracardiac PMI.

Results From the Sensitivity Analyses

In the complete-case sensitivity analysis (n=1829), including only cases with complete hs-cTnT measurements preoperative and on the first 2 postoperative days, the adjusted HR for 30-day mortality of PMI was 2.8 (95% CI, 1.6–5.2).

In the later PMI censoring sensitivity analysis (n=2018), censoring patients if they had a repeat surgery leading to a PMI, we found the 30-day mortality HR of PMI to be 3.2 (95% CI, 1.8–5.8).

Table 3. Multivariable Cox Proportional Hazards Model for 30-Day and 1-Year Mortality After PMI

	HR 30-Day Mortality	P Value	HR 1-y Mortality	P Value
Model with PMI				
PMI	2.73 (1.54–4.84)	0.001	1.58 (1.16–2.15)	0.003
Age, y	1.06 (1.03–1.10)	0.001	1.05 (1.04–1.07)	<0.001
Nonelective surgery	3.07 (1.69–5.57)	<0.001	1.42 (1.08–1.86)	0.013
RCRI	1.34 (1.03–1.74)	0.031	1.57 (1.38–1.79)	<0.001
Sepsis	5.59 (2.99–10.47)	<0.001	2.60 (1.67–4.04)	<0.001
Stroke	3.10 (1.16–8.32)	0.024	2.64 (1.34–5.20)	0.005
Pneumonia	2.69 (1.28–5.63)	0.009	2.36 (1.54–3.63)	<0.001
Model with PMI subtypes				
Cardiac PMI	2.28 (1.19–4.36)	0.013	1.48 (1.07–2.06)	0.019
Noncardiac PMI	4.44 (1.85–10.63)	0.001	2.27 (1.20–4.27)	0.011
Age, y	1.07 (1.03–1.10)	<0.001	1.06 (1.04–1.07)	<0.001
Nonelective surgery	2.89 (1.57–5.31)	0.001	1.38 (1.05–1.83)	0.021
RCRI	1.36 (1.04–1.77)	0.024	1.58 (1.39–1.80)	<0.001
Sepsis	4.45 (2.15–9.19)	<0.001	2.33 (1.44–3.78)	0.001
Stroke	2.37 (0.82–6.88)	0.113	2.38 (1.18–4.81)	0.016
Pneumonia	2.85 (1.34–6.04)	0.006	2.37 (1.54–3.64)	<0.001

Data are shown for models including PMI and including PMI split into cardiac and extracardiac subtypes. Data are shown as HRs with 95% confidence interval. HR indicates hazard ratio; PMI, perioperative myocardial injury; and RCRI, revised cardiac risk index.

Association of hs-cTnT With 30-Day Mortality

In our cohort, 1261 (51%) of all patients already had preoperatively hs-cTnT levels at or above the 99th percentile of 14 ng/L, with patients with PMI showing an even higher proportion of 80% (Table 4). One thousand nine hundred thirty-six of 2546 (76%) patients had an increase of hs-cTnT levels postoperative in comparison with preoperative values, with the median increase in the total population being 3 ng/L (IQR, 1–8; Table 4). Postoperatively, 1626 of 2546 (64%) patients had a postoperative level \geq 99th percentile of 14 ng/L.

When plotting 30-day mortality according to absolute hs-cTnT increase and maximum postoperative hs-cTnT levels, both plots indicated rather stable low mortality rates for very low delta (\leq 5 ng/L, 68% of the cohort) and low maximum values (\leq 10 ng/L, 25% of the cohort). Although, for maximum postoperative hs-cTnT values, this was followed by a gradual near-linear increase, the association between hs-cTnT increase and mortality seemed to exhibit different slopes $>$ 5 ng/L (Figure 3).

When evaluating the interaction of preoperative hs-cTnT elevations and PMI, we found that PMI was associated with a worse outcome irrespective of preoperative

values, but overall mortality was higher in patients with preexisting preoperative hs-cTnT elevations above the 99th percentile (Figure 4).

DISCUSSION

This diagnostic study using central adjudication was embedded within a PMI-screening program implemented as part of routine clinical practice and aimed to contribute to a better understanding of PMI as an often neglected and underestimated complication after noncardiac surgery.^{7,8} We report 6 major findings.

First, the incidence of PMI after noncardiac surgery detected during routine clinical screening in patients at increased cardiovascular risk is very high. One of 7 patients $>$ 65 years of age or with preexisting coronary artery disease, peripheral artery disease, or stroke developed PMI. These findings extend and corroborate previous work on PMI, particularly the VISION study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation).^{1,3–5,9} The incidence of PMI observed in our study was comparable to that observed, eg, in VISION if using a comparable absolute hs-cTnT-delta criterion.^{1,3–5,9} Differences in observed incidence rates found in several previous studies seem to relate to differences in the study populations, definitions of PMI, and the cTn assays used.^{1,3–5,9} The VISION study included patients $>$ 45 years (mean age, 63 years) irrespective of preexisting coronary artery disease or peripheral artery disease, and therefore at lower cardiovascular risk than in this study (median age, 74 years). Accordingly, 30-day mortality in this study was twice that observed in VISION. In VISION, multiple cutoff values of maximum postoperative hs-cTnT levels defining an event were retrospectively chosen, with, eg, \geq 20 ng/L resulting in a PMI incidence of 17.9%.⁵ In our cohort, median preoperative hs-cTnT concentration was 14 ng/L, and the median maximum postoperative concentration in patients adjudicated to have PMI was 64 ng/L. Regarding the definition of PMI, the high frequency of elevated hs-cTn plasma concentrations before surgery observed in this study (51%), VISION, and other studies clearly highlight the need for a definition that takes preoperative hs-cTn levels into consideration to avoid misclassification of chronic hs-cTn elevations as PMI.^{4,5,9,19}

Second, clinical presentation of PMI differed markedly from that of spontaneous AMI.⁸ Among patients with PMI, only 6% had typical chest pain, 18% had any ischemic symptoms, and 29% fulfilled additional criteria required for spontaneous AMI beyond the increase in hs-cTnT. These prospective observations corroborate that these acute events would in the vast majority have been missed in the absence of systematic screening.^{1–5}

Third, patients with PMI had 6 times the 30-day mortality observed in patients without PMI, despite the early

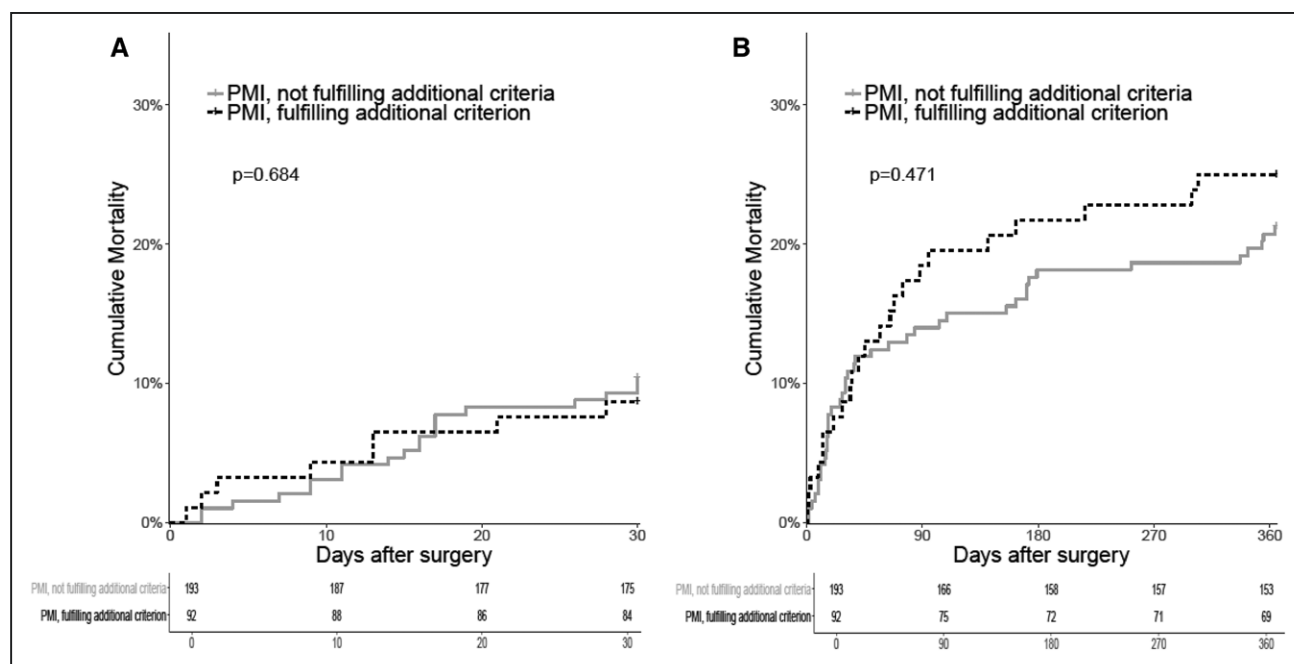


Figure 2. Perioperative myocardial injuries not fulfilling versus fulfilling additional criteria for spontaneous infarction.

Cumulative all-cause mortality within 30 days and 1 year of patients with perioperative myocardial injury (PMI), split according to whether patients not fulfilling any of the additional criteria required for the diagnosis of spontaneous acute myocardial infarction besides the cardiac troponin criterion (ischemic symptoms, or ischemic signs on ECG or on cardiac imaging) or if they fulfill at least one of the additional criteria.

detection within the clinical screening program. The excess mortality associated with PMI persisted up to 1 year.

Thirty-day mortality was comparable among patients with PMI not fulfilling any other of the additional criteria required for spontaneous AMI (ischemic symptoms, new ECG changes, imaging evidence of loss of viable myocardium) versus those with at least 1 additional criterion. Similar observations were made in VISION, adding to the ongoing controversy of what criteria should be applied in the definition of perioperative MI in addition to the documentation of acute cardiomyocyte injury.^{1,5–8,20}

Fourth, PMI associated with a primarily extracardiac disorder triggering cardiomyocyte injury such as severe sepsis has even worse prognosis with 1 of 3 patients dying within 30 days.

Fifth, acute cardiomyocyte injury occurring in the perioperative period (PMI) had additive and possibly amplifying detrimental effects on 30-day and 1-year mortality on top of chronic cardiomyocyte injury attributable to various chronic cardiovascular disorders present before the operation. Accordingly, PMI was associated with increased mortality in patients presenting with low preoperative hs-cTnT concentrations, and elevated preoperative hs-cTnT concentrations, as well. In fact, the association between the amount of cardiomyocyte injury as quantified by hs-cTnT plasma concentration and mortality seemed to be continuous. Increasing absolute hs-cTnT deltas, and increasing postoperative maximum hs-cTnT

concentrations, as well, were associated with increasing mortality rates. Although the association between postoperative maximum hs-cTnT concentrations and mortality seemed to be near linear in hs-cTnT concentrations >10 ng/L, the association between absolute hs-cTnT deltas and mortality seemed biphasic above deltas of 5 ng/L.

Sixth, after detailed review of all clinical information pertaining to the individual patient, coronary angiography was recommended by the cardiology consultant in only 10% of patients with PMI. This highlights that the dominant pathophysiological mechanisms and the associated optimal management of patients with PMI is likely fundamentally different from that of patients with spontaneous MI. In the majority of patients with PMI, cardiomyocyte injury seems to be caused by supply-demand mismatch attributable to hypotension, anemia, and tachycardia rather than plaque rupture.^{20–22} However, these patients also had high cardiovascular mortality and may benefit from intensification of medical treatment.²³

These findings extend and corroborate previous work on PMI and efforts aimed at improving outcomes after noncardiac surgery^{1,2,4–6,19} The high incidence of PMI and the high mortality rate observed in this study suggest that the specific selection criteria used to identify high-risk patients deserve to be replicated in future studies. Ideally, these should include a randomized controlled trial testing the effect of active surveillance combined with an active response protocol on clinical and economic outcomes.

Table 4. High-Sensitivity Cardiac Troponin T Levels

	Preoperative hs-cTnT, ng/L	Preoperative Values >99 th , n (%)	Maximum Postoperative hs-cTnT, ng/L	Postoperative Values >99 th , n (%)	Maximum Perioperative Δ hs-cTnT, ng/L
Total cohort	14 (8–25)	1261 (51)	18 (11–33)	1626 (64)	3 (1–8)
No PMI	12 (7–22)	957 (46)	15 (10–24)	1229 (57)	2 (0–5)
PMI	28 (16–57)	304 (80)	64 (42–131)	397 (100)	25 (17–46)
Cardiac	27 (15–51)	262 (79)	58 (41–109)	342 (100)	24 (17–43)
Extracardiac	45 (18–95)	42 (84)	114 (53–175)	55 (100)	33 (19–83)

Levels are shown with interquartile range, number above the 99th percentile (%), and maximum perioperative delta shown for all patients, those with and without perioperative myocardial injury (PMI), as well as for cardiac and extracardiac PMI subtypes. hs-cTnT indicates high-sensitivity cardiac troponin T.

Strengths

Strengths of this study include the implementation of PMI screening in clinical routine, prospective assessment of symptoms possibly associated with PMI, central adjudication, use of hs-cTnT including preoperative measurements to reliably distinguish PMI from chronic hs-cTnT elevations from chronic cardiac disorders, long-term follow-up, and very high completeness of follow-up (eg, 99.9% at 30 days).

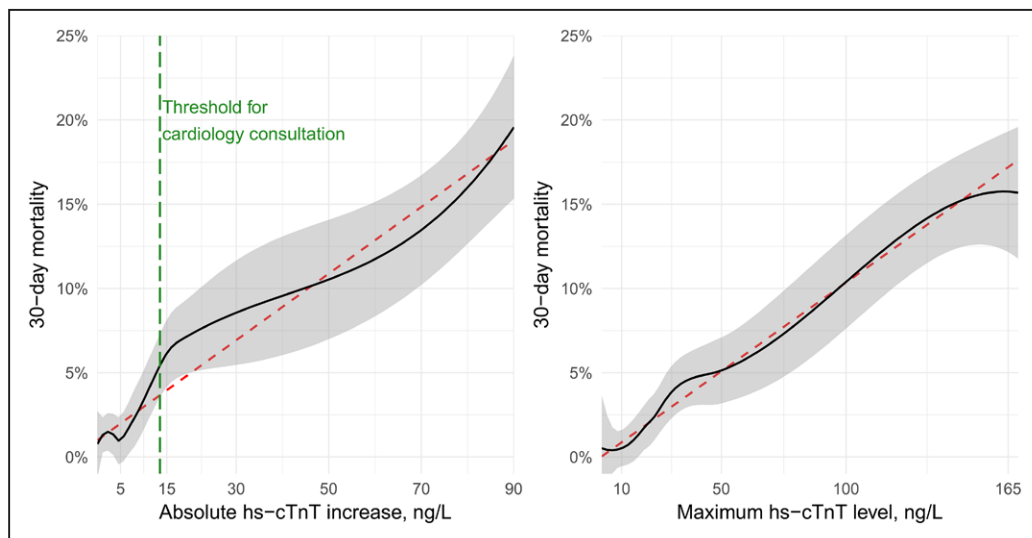
Limitations

The following limitations should be considered when interpreting these findings. First, there is no universally accepted definition of PMI. The absolute hs-cTnT change criteria used to define PMI in this study are, at large, arbitrary. Although the hs-cTn cutoff criteria for spontaneous MI (99th percentile of healthy individuals)

also are arbitrary, they are widely accepted and based on broad consensus. Our criterion for PMI is supported by recent data from VISION, but still requires approval by expert groups.⁸ Second, hs-cTnT was measured routinely in the first 2 days after surgery, and afterward only in case of clinical suspicion of MI. Therefore, a small number of asymptomatic PMIs occurring after the first days invariably were missed. Accordingly, our point estimates slightly underestimate the true incidence of PMI.^{2,5} Third, the adjudication of PMI subtypes into cardiac and extracardiac PMI was largely based on clinical criteria, because the majority of patients did not undergo coronary angiography.

CONCLUSION

PMI is a common complication after noncardiac surgery and, despite early detection during routine clinical screening, is associated with substantial short- and long-

**Figure 3. Cardiac troponin and mortality.**

Association of absolute high-sensitivity cardiac troponin T (hs-cTnT) increase and maximum postoperative hs-cTnT level with 30-day mortality (black continuous line with 95% confidence intervals in gray). A general linear fit is shown as red dashed line. Because the association of absolute hs-cTnT increases with 30-day mortality might be affected by identifying and flagging patients with perioperative myocardial injury in clinical routine at hs-cTnT deltas of ≥ 14 ng/L, this threshold was highlighted in the plot of absolute hs-cTnT increase (green dashed line).

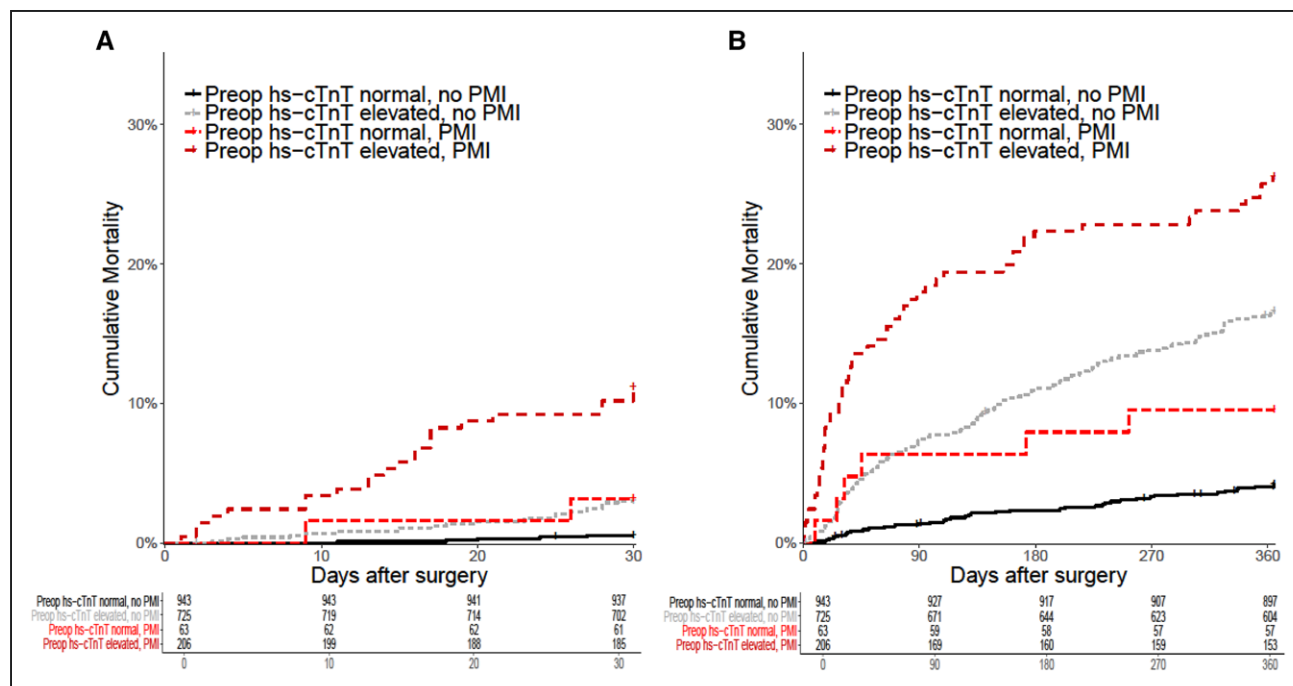


Figure 4. Mortality according to preoperative elevations of cardiac troponin and occurrence of perioperative myocardial injury.

Cumulative all-cause mortality within 30 days and 1 year of all patients stratified according to preoperative high-sensitivity cardiac troponin T (hs-cTnT) levels (above or below the 99th percentile) and occurrence of perioperative myocardial injury (PMI) after surgery (n=1937)

term mortality. Mortality seems comparable in patients with PMI not fulfilling any other of the additional criteria required for spontaneous AMI versus those who do.

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Dr Puelacher, Dr Lurati Buse, and Prof Mueller contributed to design and conduct of the study, analyzed and interpreted the data, wrote the manuscript, and had final responsibility in the decision to submit for publication. Dr Puelacher performed literature review and created the figures. Dr Puelacher, Dr Lurati Buse, Dr Wildi, and Prof Mueller had full access to the data. All authors contributed to data collection, provided critical feedback at various stages of the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Disclosures

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APPENDIX

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