Perioperative Myocardial Injury in Non-cardiac Surgery - Incidence, Patient Characteristics, Outcome, and Possible Strategies to Improve Outcome

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Summary

The global volume of surgery is steadily increasing and surgical patients are becoming older and increasingly comorbid, making the perioperative setting a common challenge for physicians. Despite substantial improvements in surgical and anaesthesiological techniques, there is still a relevant risk of dying associated with non-cardiac surgery, with 30-day mortality rates ranging from 1 to 10% depending on the patient population.

Major cardiac complications are believed to be a major contributor to this excessive mortality. In particular, perioperative myocardial injury (PMI) appears to be a major contributor and is potentially associated with one third of postoperative mortality. Initial study data have highlighted that PMI is difficult to diagnose, as typical symptoms of spontaneous acute myocardial infarction, especially ischemic chest pain, are only observed in <20% of all patients.

In order to address important gaps in knowledge of PMI, we conducted my PhD project "Perioperative Myocardial Injury in Non-cardiac Surgery – Incidence, Patient Characteristics, Outcome and Possible Strategies to Improve Outcome" (BASEL-PMI) at the University Hospital Basel. Its aim was to generate data within clinical routine to gain important insights into the incidence of PMI, its association with postoperative mortality, and to further characterise PMI.

We were able to show that PMI is surprisingly common after non-cardiac surgery, occurring in 16% or in one in seven patients. With a mortality rate within 30 days of 10% and of 23% within one year, the associated mortality increased six-fold in comparison to patients without a PMI (1.6% at 30 days, 9.3% within one year), highlighting the importance of PMI as a perioperative complication. Nonetheless, due to their asymptomatic presentation (2/3 did not show any signs or symptoms), PMI are often missed in clinical routine. This lack of appreciation of a significant postoperative complication compromises the prognostic accuracy of preoperative scores used to assess the risk-benefit of surgery.

In characterising PMI, we were able to identify two distinct subcategories of PMI, separating a "cardiac" subtype from an "extra-cardiac" subtype in which the heart is damaged by a systemic pathology such as severe sepsis. Furthermore, we were able to show that PMI is associated with an increased mortality independent of the ischemic symptoms or of whether the signs are present or not (8.7% vs 10.4%).

Finally, we made our first tentative steps towards the hypothesis that systematic screening for PMI might improve outcome.

Deutsche Zusammenfassung

Mit einer stetig zunehmenden Zahl an Operationen an immer älteren Patienten ist das perioperative Setting ein wichtiger Aspekt der modernen Medizin geworden. Trotz konstanter Entwicklung im Bereich der Anästhesie- sowie der chirurgischen Technik sind nicht-kardiale Operationen noch immer mit einem relevanten Risiko verbunden und je nach Kollektiv versterben 1-10% der Patienten innerhalb von 30 Tagen.

Als ein wichtiger Faktor für diese Übersterblichkeit werden kardiale Komplikationen vermutet. Besonders perioperative Herzmuskelschädigungen (PMI) scheinen eine wichtige Rolle zu spielen und mit bis zu einem Drittel der Sterblichkeit assoziiert zu sein. In ersten Studien zeigte sich allerdings, dass die Diagnose solcher PMI schwierig ist, da das Kardinalsymptom des spontanen Herzinfarkts, die typischen Symptome wie v.a. Brustschmerz, in <20% der Patienten auftreten.

Um bestehende grosse Wissenslücken über die wenig beschriebenen PMI zu adressieren, wurde mein PhD-Projekt „Perioperative Myocardial Injury in Non-cardiac Surgery - Incidence, Patient Characteristics, Outcome, and Possible Strategies to Improve Outcome“ (BASEL-PMI) am Universitätsspital Basel initiiert. Ziel war es in der klinischen Routine Daten zu generieren über die Häufigkeit des Auftretens von PMI, ihren Zusammenhang mit der vermehrten postoperativen Sterblichkeit zu untersuchen und PMI besser zu beschreiben.

In unsrer Studie zeigte sich, dass PMI erstaunlich häufig sind mit einer Inzidenz von 16%, also in einem von sieben Patienten auftritt. Mit einer Sterblichkeit von 10% in 30 Tagen und 23% innerhalb eines Jahres, war die Übersterblichkeit dieser Patienten sehr hoch im Vergleich zu den Patienten ohne PMI (1.6% und 9.3%%), was die Bedeutung des PMI als perioperative Komplikation unterstreicht. Aufgrund ihrer meist symptomfreien Präsentation (2/3 zeigten keinerlei Symptome oder Zeichen), werden PMI in der klinischen Routine oft nicht erkannt. Durch die fehlende Erkennung dieser wichtigen postoperativen Komplikation ist die prognostische Wertigkeit präoperativer Risikoscores, welche zur Risiko-Nutzen-Einschätzung chirurgischer Eingriffe genutzt werden, kompromittiert.

Wir konnten zwei distinkte Subkategorien von PMI identifizieren, wobei wir „kardiale“ PMI abgrenzten von „extra-kardialen“ PMI, bei denen eine Erkrankung ausserhalb des Herzens als Hauptproblem das Herz in „Mitleidenschaft“ zieht. Eine zentrale Erkenntnis war weiteres, dass PMI unabhängig davon ob sie ischämietypische Symptome oder Zeichen zeigen oder nicht mit einer ähnlich erhöhten Mortalität (8.7% vs 10.4%) assoziiert waren.

Bei der Analyse unsrer Daten konnten wir auch Hinweise darauf finden, dass das perioperative Screening nach PMI die Übersterblichkeit reduzieren könnte.

Introduction

Worldwide, over 300 million major surgical procedures are performed annually, translating to one procedure for every 25 human beings[1,2]. In resource-rich countries like Switzerland, the incidence increases to as high as ~1 surgical procedure for every 10 citizens (~900.000 per year in Switzerland)[1]. Despite advances in all fields of medicine, there is still a significant risk of death related to major non-cardiac surgical procedures. The observed 30-day mortality depends on patient as well as procedural factors and ranges from 1% to 10%[3–10].

Perioperative major adverse cardiac events (MACE) and, in particular, perioperative myocardial injury (PMI) have only recently received scientific attention as a possible contributor to these perioperative deaths[6,7,11].

Perioperative myocardial injury differs in several aspects from spontaneously occurring acute myocardial infarction (AMI) presenting to the emergency department. One of the key differences seems to be that the vast majority of patients experiencing PMI do not show any typical ischemic symptoms, e.g. chest pain[3,4,6,8–10,12]. The reasons for this are not fully understood, but may include intense analgesia following surgery and possibly also different pathophysiological mechanisms underlying PMI[11,13–16]. Only in a minority of cases does PMI show any ischemic changes on the electrocardiogram (ECG), and such changes present in only 35% of patients[7]. As a consequence of this lack of typical symptoms and signs, most patients with PMI are currently not detected in routine clinical practice[3,4].

In spite of its silent manifestation, PMI is strongly associated with mortality. First studies estimated that PMI appeared to be a major contributor to 34–42% of all deaths within 30 days of non-cardiac surgery[3,7]. It is important to note that the 30-day mortality of patients with PMI was similar for those who were asymptomatic and those who had ischemic symptoms (30-day mortality 12.6% in asymptomatic vs 9.8% in symptomatic patients, p=0.84)[6].

Symptoms and ECG changes are two important building blocks in the diagnosis of spontaneous AMI, according to current guidelines[17], but the most important, and sine qua non feature is an elevated and dynamic value of cardiac troponin (cTn). Cardiac troponin T and I are cardiomyocyte-specific proteins which play an essential role in the contraction of the cardiac muscle[18]. Their function is to translate the excitation signal into contraction of the actin and myosin filaments. As they are only expressed in heart muscle cells, they are markers with high specificity for myocardial damage[17,19–21]. The introduction of high-sensitivity cTn (hs-cTn), assays able to measure cTn values in >50% of the population with adequate precision[22], has been a significant improvement and has allowed the detection and quantification of myocardial injury at much lower thresholds[17,23,24].

As the symptoms and the ECG lack reliability, international guidelines[17,25,26] have begun to recommend routine monitoring of cTn in high-risk patients, both prior to and for 48–72 hours after major non-cardiac surgery. Implementing this monitoring as a systematic screening process appears necessary, as using only cTn measurements when deemed clinically indicated resulted in a three-fold lower rate of PMI detection when compared to systematic screening in a previous study[4].

Myocardial injury after non-cardiac surgery

As a first step, the concept of "myocardial injury after non-cardiac surgery" (MINS) has been proposed for the perioperative setting[7]. In contrast to the diagnosis of spontaneous AMI, the diagnosis of MINS took into account the asymptomatic presentation of PMI and was based solely on cTn[7,17].

A conventional cTnT assay was used in the Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) study enrolling 15000 patients up to 2011. This study found that the 30-day mortality of patients was associated with postoperative peak cTn, ranging from 1% at the lowest cTnT values (<10 ng/l) to 17% in the highest (>300 ng/l) group[3]. MINS was then defined as any postoperative cTnT value of ≥30ng/L. This resulted in an incidence of 8% and an adjusted odds ratio (aOR) of 3.9 (95% confidence interval (95%CI) 2.9–5.3) for death within 30 days following MINS.

Unfortunately, the definition "MINS" has a significant shortcoming as it relies only on postoperative measurements: it cannot distinguish between acute and chronic elevations of cTn. Cardiac troponin is known to be elevated in multiple chronic cardiac diseases, e.g. stable coronary artery disease, chronic heart failure, or atrial fibrillation[27–29], and this would lead to a significant proportion of patients (especially in the aging comorbid surgical population) being classified as having MINS simply by reason of pre-existing chronic elevations. This was shown in a subgroup of the VISION population, where 22% had already had preoperative elevations in hs-cTnT, despite being a relatively healthy cohort (mean age 65 years, 82% Revised Cardiac Risk Index ≤1)[30]. Such elevations have previously been shown to be independently associated with increased risk of death and MACE[31]. In actual fact, these patients did not experience an acute event that required any intervention and were hence at risk of overtreatment following an incorrect diagnosis of an acute disease.

PMI Definition

It is clear that a definition implementing this information about preoperative hs-cTn levels would be desirable to identify only acute events time-related to surgery, thus avoiding misclassification of chronically elevated levels. Such a definition could use delta values

instead of absolute postoperative levels. When diagnosing AMI in the non-surgical setting, absolute changes were shown to have a higher diagnostic accuracy when compared to relative changes[32,33]. In addition, from a scientific standpoint a definition using measurements pre- and postoperatively is essential if one is to be sure that an event is time-related to surgery and in order to draw conclusions about predisposing factors and potential pathophysiology of PMI.

As a result of our limited understanding of PMI, no data on potential thresholds for absolute change of hs-cTn existed when this study commenced. The current definition for spontaneous AMI states that AMI should be diagnosed if a patient's hs-cTn values show a dynamic profile and if the values at any time exceed the 99th percentile of values found in a healthy reference population[17].

We chose therefore to define PMI prospectively, and differently from MINS, as an absolute increase in hs-cTnT. We set the absolute increase needed for diagnosis of PMI to ≥14 ng/L, as 14 ng/L represents the 99th percentile of healthy individuals for the hs-cTnT assay[22]. In this way all PMIs would consistently fulfil the change as well as the absolute cTn criteria of the universal definition[17].

This decision was further corroborated by very recent data that became available in 2017, in which the MINS criteria were adapted after the introduction of hs-cTnT to the VISION study to include an additional criterion of an absolute change of ≥5 ng/L hs-cTnT for all postoperative values of hs-cTnT below 65 ng/L[12].

Gaps in research

Incidence of PMI

In the perioperative setting, myocardial infarction is believed to be a rare but dangerous event, occurring in 1%[34–36] of patients undergoing non-cardiac surgery. From new study data we learned that PMI is often missed as a result of its commonly asymptomatic presentation and is much more common than currently seen in clinical routine. In observational studies PMI rates were reported to vary considerably, ranging from 6–73%[3,5,30,37]. This broad range of estimates stems from different study populations, different definitions of PMI and different cTn assays. In the most recent publication of the VISION study[12], which enrolled patients older than 45 years, only postoperative measurements of conventional cTn were used to define MINS, and events accompanied by acute non-cardiac conditions were excluded. The multiple cut-off values defining an event were retrospectively chosen, with the lowest cut-off (at ≥20 ng/L) resulting in an incidence of PMI of 17.9%[12]. In a subset of the same study, the VISION-Biobank, hs-cTnT was measured pre- and postoperatively and PMI was defined as a

relative change to baseline of ≥85%, resulting in a markedly higher incidence of 22%[30]. In a study that included patients older than 60 years undergoing moderate to high-risk surgery, PMI was defined as elevations ≥60 ng/L in conventional cTnI, resulting in an incidence of 19%[5].

This heterogeneity of results and the fact that nearly all were collected from observational study data underlined the need for a study using a prospective definition of PMI and a research setting integrated into routine clinical practice in order to generate an estimate that would be useful for clinical practice.

Preoperative risk stratification

Lack of appropriate detection of PMI and thereby overall major adverse cardiac events (MACE) in routine clinical practice also raises questions about the utility and accuracy of presently available clinical risk scores[25,35,38,39]. All currently recommended scores, e.g. the Revised Cardiac Risk Index (Lee score)[35] or the recently developed American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator[39] were derived from studies without systematic perioperative screening, therefore capturing only symptomatic events or asymptomatic chance findings. This is particularly detrimental as both more accurate preoperative identification of high-risk patients and more precise and reliable early detection of MACE with initiation of therapy might have the potential to contribute to a reduction in perioperative mortality rates.

One method with which to quantify the perioperative risk of MACE or death could be the use of hs-cTn. Conventional cTn assays have lacked prognostic accuracy, but the transition to hs-cTn offers potential for prediction, as shown by a study in which prognostic value was quantified by area under the receiver operating characteristics curve (AUC); this was 0.56 (95%CI not given but including 0.5) for conventional cTnI and 0.69 (95%CI 0.60-0.78) using hs-cTnT[40]. Data from a vascular surgery cohort suggest that preoperative hs-cTnT measurements provide additional prognostic information to the Lee score in the prediction of AMI and death[41]. In a study enrolling non-cardiac surgery, hs-cTnT was also shown to be an independent predictor of MACE, including all-cause death[31]. Prognostic accuracy was moderate for the prediction of MACE (AUC 0.78), and superior to a commonly used risk score, the Lee score (AUC 0.68). Prognostic accuracy was also numerically higher than B-type natriuretic peptide (AUC 0.71), an alternative biomarker in the perioperative setting[31].

To date, no study has evaluated hs-cTnI for the prediction of postoperative complications, and therefore no data on the comparison of both markers for preoperative risk stratification exist. It can be hypothesised that these markers might behave in like manner, but pilot

studies have also highlighted potential confounders of hs-cTn levels, which appear to be different for the cTnT and cTnI molecules[42,43].

Pathophysiology of PMI

The predominant pathophysiology of PMI is currently unknown[11,13,44,45]. In patients presenting with spontaneous AMI, atherosclerotic plaque rupture and/or erosion with formation and often distal embolization of a thrombus, referred to as type I, is the dominant pathophysiological mechanism[17]. Initial pilot studies showed that only 50% of PMI may have been caused by plaque rupture and thus regarded as type I[13,44,45]. But as these studies recruited only a small minority of symptomatic PMI patients (~20%[3]), results might be biased towards inclusion of type I PMIs.

It has been hypothesized that type II MI, characterized by a supply-demand mismatch of oxygen, and not type I MI, characterized by acute thrombotic coronary occlusion, might be the predominate mechanism of PMI[11]. This has been suggested as the perioperative setting is characterized by multiple factors associated with type II infarctions, e.g. imbalance of oxygen as a result of hypotension[46–49], tachycardia[16,50], hypoxemia[51], or anaemia[14], and potentially also sympathetic activation[52] or hypothermia[53].

It is important to highlight the fact that acute extra-cardiac pathologies other than type II MI can affect the heart, as for example severe sepsis, which has been shown to cause cardiomyocyte injury without evidence of coronary artery disease[54,55].

Further characterization of the causes of PMI has enormous clinical consequences as type I AMI, for instance, has been shown to benefit from aggressive anticoagulation, platelet inhibition and early coronary revascularisation[17,56], while these treatments may harm patients with PMI as a result of an increase in bleeding complications, especially detrimental in the perioperative period.

Potential strategies to improve outcome of PMI

Considering the worldwide volume of 300 million surgeries[1,2], and assuming that a third of these are at elevated risk and that the incidence of PMI is 8%[3,5,30,37], a total of eight million patients suffer a PMI every year, increasing their 30-day mortality almost four-fold. Strategies focusing on improving the outcome of PMI could therefore translate into considerable health gains, making high quality research on this issue extremely relevant.

Related to our incomplete understanding of the incidence and pathophysiology underlying PMI, specific recommendations for treatment or prevention are currently lacking. This is a particular concern with regard to procedures and therapies associated with relevant peri-

procedural risk such as coronary angiography and coronary revascularization, but also dual-antiplatelet therapy inherently associated with increased bleeding.

It is as yet unclear whether the use of current cardiovascular medication including statins, angiotensin-converting-enzyme-inhibitors/angiotensin II receptor-blockers, and beta-blockers might have the same beneficial effects on PMI as they do on AMI. Observational data from the neutral POISE study implied that use of acetylsalicylic acid or of statins was associated with a reduction in 30-day mortality (aOR 0.54, 95%CI 0.29 to 0.99 and aOR 0.26, 95%CI 0.13 to 0.54 for statins)[6]. In a retrospective study in vascular patients, intensification of medical therapy according to the treatment recommendations for stable coronary artery disease[57] was associated with a three-fold decrease in risk of major adverse cardiac events in one year in patients with a PMI[58]. In contrast, a small randomized controlled study of 70 patients showed no that there were no benefits for one-year survival (17% vs 17%, p=1.0)[59] associated with transferring patients with cTnI-elevations to the cardiology ward rather than to the surgical ward. However, results from this study should be viewed with caution as it was carried out without a standard protocol of any interventions besides transfer to the cardiology ward and was based on highly unrealistic assumptions of the power calculation (absolute risk reduction in one-year mortality of 20%, from 35% to 15%)[59].

Related to the successes of preventive strategies in cardiac diseases in the non-surgical setting, research focusing on the prevention of PMI could be another very relevant area of study. In a pilot study, Ausset et al.[60] showed that focusing on improving postoperative care to prevent PMI reduced one-year mortality from 8% to 2%. Measures taken were multiple, driven by a risk analysis followed by a complete overhaul of the processes in the researchers' surgical ward[60]. As this was a single-centre open crossover study, a Hawthorne effect cannot be excluded. If we are to develop more targeted strategies, our understanding of the pathophysiology of PMI needs to be enhanced.

Rationale of our study

Overall, we saw a need for further research in the field of PMI that would have the potential to improve perioperative care. In the years since 2014 a growing number of studies has begun to add to our understanding of PMI, especially its incidence and outcome, but many questions remain unanswered. Data from this PhD project could make a significant contribution to addressing these questions.

Aims

The primary aim of this project was to evaluate the incidence, outcome and characteristics of PMI in patients undergoing major non-cardiac surgery:

1. Evaluate the incidence of PMI following major non-cardiac surgery
2. Evaluate the association of PMI with all-cause death at 30 days and one year
3. Describe subtypes of PMI and their association with all-cause mortality at 30 days and one year
4. Evaluate the impact of PMI not fulfilling any additional criteria besides the troponin criterion necessary for diagnosis of spontaneous AMI[17]

Further, the aims were to establish a large prospective cohort to address questions concerning the incidence of other MACE, evaluate current risk scores and describe the role of hs-cTn in preoperative risk scoring.

5. Evaluate the incidence of MACE after non-cardiac surgery
6. Evaluate established clinical risk scores for the detection of MACE
7. Evaluate the prognostic utility of preoperative and postoperative hs-cTn in the prediction of all-cause death and MACE

Publications

I Perioperative myocardial infarction injury after non-cardiac surgery: incidence, and mortality and impact of cardiology consultation

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Abstract

Background: Perioperative myocardial injury (PMI) seems to be a contributor to mortality after non-cardiac surgery. As 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 non-cardiac surgery that 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 (hs-cTnT) in clinical routine. PMI was defined as an absolute hs-cTnT increase of ≥14 ng/L from preoperative to postoperative measurements. Further, 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 (AMI) versus those that did.

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

Conclusion: PMI is a common complication following non-cardiac 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 AMI versus those that do.

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 non-cardiac surgery occurring in one out of seven patients. Only 6% of patients with PMI experience typical chest pain, clearly indicating major differences to spontaneous myocardial infarction. PMI is associated with substantial 30-day and one-year mortality (9% and 22%), with similar mortality in patients with PMI not fulfilling the additional criteria for spontaneous myocardial infarction criteria versus those that do.

What are the clinical implications?

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

Introduction

Perioperative myocardial injury (PMI) has recently been identified as an important yet often undetected complication following non-cardiac surgery, strongly associated with 30-day-mortality[3,5,6,12,37]. In contrast to 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 US and worldwide[3,5,6,12,37].

Considering more than 300 million surgeries are performed annually and demographic change is resulting in an increasing number of surgical patients with elevated cardiovascular risk, strategies improving the detection, treatment and outcome of PMI would seem to have an enormous potential to provide 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. As electrocardiography (ECG) also has very low sensitivity[7], the detection and quantification of acute cardiomyocyte injury by measuring cardiac troponin (cTn) is critical for the clinical diagnosis of PMI[17,25].

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 due to PMI by using preoperative and postoperative hs-cTn measurements[30]. The differentiation between PMI and chronic elevations in hs-cTn due 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 non-cardiac surgery for PMI[17,25], our institution initiated a PMI screening program with a structured response system embedded within clinical routine. The aim of the present study was to 1) assess the incidence of PMI detected by a screening program implemented into clinical routine, which included both pre- AND postoperative measurements of hs-cTnT; 2) evaluate its association with 30-day and one-year-mortality.

Methods

We adhered to the STROBE reporting guidelines, with further information found in the Supplement.

Patients

We included consecutive patients undergoing non-cardiac 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. As 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 non-cardiac surgery. Patients were screened if they had a planned hospital stay exceeding 24h after surgery and were considered at increased mortality-risk defined as ≥65 years of age, OR ≥45 years with history of coronary artery disease (CAD), peripheral arterial disease (PAD), or stroke. Plasma concentrations of hs-cTnT were measured within 30 days prior to 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 high-sensitivity cardiac troponin T (hs-cTnT) measurements were ordered by the treating anaesthesiologist. Patients underwent hs-cTnT monitoring and were registered into the database multiple times if a minimum of 5 days had elapsed between procedures.

Endpoints

PMI was prospectively defined as an absolute increase in hs-cTnT of ≥14 ng/L above preoperative values (or between two postoperative values if the preoperative value was missing) within seven days of surgery. Based on findings from prior studies showing that asymptomatic elevations in cTn were also associated with increased short-term mortality[3], 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[61], and were previously shown to be independently associated with increased risk of death and major adverse cardiac events[31].

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 as compared to relative changes in the detection of acute MI in the non-operative setting[32,33]. The absolute increase of ≥14 ng/L was selected as 14 ng/L represents the 99th percentile of healthy individuals and thereby all PMIs invariably would fulfill the change as well as the absolute cTn criteria required for the diagnosis of spontaneous AMI[17].

PMI was centrally adjudicated by two 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: “extra-cardiac” in which a primarily extra-cardiac disease such as severe sepsis, stroke, or pulmonary embolism triggered PMI, and “cardiac” for all other cases. In cases of disagreement between the two 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[17]. As all PMI necessarily fulfilled the cTn criteria, one or more of the following was required: 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 new loss of viable myocardium or new regional wall motion abnormality, identification of an intracoronary thrombus by angiography or autopsy[17]. The primary event-related prognostic endpoint was 30-day-mortality and one-year-mortality was the secondary prognostic endpoint. Deaths were classified as cardiovascular or non-cardiovascular according to recent guidelines[62]. Cardiovascular death included death due to acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage (e.g. ruptured aortic aneurysm or dissection), and pulmonary embolism. All deaths were assumed to be cardiovascular in nature unless evidence of a non-cardiovascular cause was available. Non-cardiovascular death included all deaths due to a clearly documented non-cardiac and non-vascular cause, such as respiratory failure (excluding cardiogenic pulmonary edema), infections/sepsis, neoplasm, trauma (including suicide and homicide), and surgical or gastrointestinal bleeding[62].

Procedures

In case of an absolute increase in hs-cTnT of ≥14 ng/L above preoperative levels, structured response included assessing identified PMI patients 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. In order 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 due 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, as these patients already receive 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 following PMI were continuously instructed in a predefined management scheme for PMI (**Supplement Figure 1**). 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, <24h hospital stay, surgery involving the heart), had their surgery cancelled, had cardiac surgery or myocardial infarction within 14 days before surgery, if only one hs-cTnT 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 one-year-mortality", we included every patient only once at first enrollment (**Supplement Figure 2**).

Data collection

The Revised Cardiac Risk Index (RCRI) was calculated for all patients[35]. The cardiovascular risk of surgery was classified as proposed by the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) (ESC/ESA-surgical risk)[25]. During the hospitalisation 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 one 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 using an Elecsys (Roche Diagnostics) assay with limit of detection of 5ng/L, a 10% coefficient of variation at 13ng/L and the 99th percentile of a healthy reference population at 14 ng/L[22]. Hs-cTnT was measured in the 30-days preoperatively, with 83% being measured within one day prior to surgery and 94% being measured within 3 days prior to surgery.

Statistical analysis

The incidence of PMI was calculated with 95% confidence intervals (95%CI) by the method proposed by Agresti[63]. PMI incidence was stratified by surgical disciplines, ESC/ESA surgical risk[25], and postoperative stay on a regular ward or the ICU. The association of PMI with crude all-cause-mortality was evaluated 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 four groups according to baseline troponin (low versus elevated) and PMI (acute perioperative elevation present or not). To determine adjusted hazard ratios (HR), we performed multivariable regression analyses with time to all-cause death as dependent variable. After evaluation of Schoenfeld residuals, a Cox Proportional Hazards model was chosen, and the HR for PMI and its subtypes were calculated adjusted for the predefined co-variables age, non-elective surgery, RCRI, 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[64].

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 analysed cohort (**Supplement Table 1**).

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 two postoperative days (“complete case model”), and b) censoring all patients if they had a repeat surgery leading to a PMI within 30 days at 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 seven days of surgery with 30-day mortality, we plotted 30-day mortality

according to 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 (“survival”, “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 (**Supplement Figure 2**).

Incidence of PMI

PMI occurred after 397/2546 surgeries (16%, 95%CI 14-17%). Patients with PMI had more cardiovascular comorbidities and consequently a higher RCRI, and a higher rate of non-elective surgery (**Table 1**). The incidence of PMI increased with higher ESC/ESA-risk category of the surgical procedure from 9% in the lowest to 25% in the highest category (**Supplement Table 2**). 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, 325/397 (82%), did not show any ischemic symptoms, and chest pain was only present in 24/397 (6%). ECG findings suggestive of myocardial ischemia, especially ST-segment depression or T-wave inversion, were observed in 60/244 (24%) of ECGs performed. Together with an additional 7 patients showing evidence of loss of viable myocardium on imaging, overall only 117/397 (29%) of patients fulfilled any of the additional criteria required for spontaneous AMI (**Table 2**).

PMI subtypes

342/397 PMI (86%, 95%CI 82-89) were classified as primarily “cardiac” and 55/397 (14%, 95%CI 10-18) as primarily “extra-cardiac” subtypes. The causes for primarily “extra-cardiac” PMI were severe sepsis or uncontrolled infection in 40/55 patients. The proportion of “extra-cardiac” 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 one-year follow-up in 99.6% of patients. Overall, 56/2018 patients (2.8%, 95%CI 2.1-3.6) died within 30 days; 23 (41%, 95%CI 29-54) due to cardiovascular and 33 (59%, 95%CI 46-71) due to non-cardiovascular causes. One year after surgery, 224/2018 (11.2%, 95%CI 9.8-12.7) patients died, 71 (32%, 95%CI 26-38) due to cardiovascular and 153 (68%, 95%CI 62-74) due to non-cardiovascular causes. Data on the surgical course and hospital stay can be seen in **Supplement Table 3**, and number of cardiology consultations, cardiac imaging, and changes in cardiovascular medication can be seen in **Supplement Table 4**.

At 30 days, 28/285 (9.8%, 95%CI 6.8-14.0) patients with PMI versus 28/1733 (1.6%, 95%CI 1.1-2.4, p<0.001) patients without PMI had died (**Figure 1A**). Cardiovascular death occurred in 14/285 (4.9%, 95%CI 2.8-8.2) patients with PMI compared to 9/1733 (0.5%, 95%CI 0.3-1.0) patients without PMI.

At one-year, 64/285 (22.5%, 95%CI 17.9-27.8) patients with PMI versus 160/1733 (9.3%, 95%CI 8.0-10.8, p<0.001) patients without PMI had died (**Figure 1B**). Cardiovascular death occurred in 26/285 (9.1%, 95%CI 6.2-13.2) patients with PMI compared to 45/1733 (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 one-year-mortality (**Table 3**).

PMI patients not fulfilling additional criteria required for spontaneous AMI had comparable 30-day mortality and one-year mortality versus PMI patients fulfilling one or more 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 15/245 (6.1%, 95%CI 3.6-10.0) versus 13/40 (32.5%, 95%CI 19.8-48.4, p<0.001, **Figure 1C+D**) in patients with PMI of “cardiac” and “extra-cardiac” subtype, respectively. In the group of patients with cardiac PMI, 60% of deaths within 30 days of surgery were cardiovascular, compared to 39% in patients with extra-cardiac subtype.

At one year, 49/245 (20%, 95%CI 15-26) patients with a cardiac PMI versus 15/40 (38%, 95%CI 24-53) patients with an extra-cardiac PMI had died. In the group of patients with cardiac PMI 43% of deaths within one year of surgery were cardiovascular, compared to 33% in patients with extra-cardiac 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 two 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).

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 PMI patients showing an even higher proportion of 80% (**Table 4**). 1936/2546 (76%) patients had an increase of hs-cTnT levels postoperative compared to preoperative values, with the median increase in the total population being 3 ng/L (IQR 1-8, **Table 4**). Postoperatively, 1626/2546 (64%) patients had a postoperative level at or above the 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 (≤5 ng/L, 68% of the cohort) and low maximum values (≤10 ng/L, 25% of the cohort). While 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 above 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 following non-cardiac surgery[17,25]. We report six major findings.

First, the incidence of PMI following non-cardiac surgery detected during routine clinical screening in patients at increased cardiovascular risk is very high. One out of seven patients above the age of 65 years or with preexisting CAD, PAD, or stroke developed PMI. These findings extend and corroborate previous work on PMI, particularly the Vascular events In non-cardiac Surgery patIents cOhort evaluatioN (VISION) study[3,5,12,30,37]. The incidence of PMI observed in our study was comparable to that observed e.g. in VISION if using a comparable absolute hs-cTnT-delta criteria[3,5,12,30,37]. 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[3,5,12,30,37]. The VISION study included patients older than 45 years (mean age 63 years) irrespective of preexisting CAD or PAD, and therefore at lower cardiovascular risk as compared to this study (median age 74 years). Accordingly, 30-day mortality in this study was twice that observed in VISION. In VISION, multiple cut-off values of maximum postoperative hs-cTnT levels defining an event were retrospectively chosen, with e.g. ≥20ng/L resulting in a PMI incidence of 17.9%[12]. 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 64ng/L. Regarding the definition of PMI, the high frequency of elevated hs-cTn plasma concentrations prior to 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 in order to avoid misclassification of chronic hs-cTn elevations as PMI[5,12,30,65].

Second, clinical presentation of PMI differed markedly from that of spontaneous AMI[17]. Among PMI patients, 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[3,5,6,12,37].

Third, patients with PMI had six-times the 30-day-mortality observed in patients without PMI, despite the early detection within the clinical screening program. The excess mortality associated with PMI persisted up to one year.

30-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 one additional criterion. Similar observations were made in VISION, adding to the ongoing controversy of what criteria should be applied in the definition of perioperative myocardial infarction in addition to the documentation of acute cardiomyocyte injury.[3,7,12,17,25,56]

Fourth, PMI associated with a primarily extra-cardiac disorder triggering cardiomyocyte injury such as severe sepsis has even worse prognosis with one out of three 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 one-year mortality on top of chronic cardiomyocyte injury due to various chronic cardiovascular disorders present prior to the operation. Accordingly, PMI was associated with increased mortality in patients presenting with low preoperative hs-cTnT concentrations as well as elevated preoperative hs-cTnT concentrations. 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 as well as increasing postoperative maximum hs-cTnT concentrations were associated with increasing mortality rates. While the association between postoperative maximum hs-cTnT concentrations and mortality seemed to be near linear in hs-cTnT concentrations above 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 PMI patients. 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 due to hypotension, anemia, and tachycardia rather than plaque rupture[11,13,56]. However, these patients also had high cardiovascular mortality, and may benefit from intensification of medical treatment[58].

These findings extend and corroborate previous work on PMI and efforts aimed at improving outcomes after non-cardiac surgery[3,5–7,12,65] The high incidence of PMI and the high mortality rate observed in this study suggests 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.

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 pre-operative 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 (e.g. 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 is at large arbitrary. While the hs-cTn cut-off criteria for spontaneous MI (99th percentile of healthy individuals) also is arbitrary, it is 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 two days after surgery, and afterwards 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[6,12]. Third, the adjudication of PMI subtypes into “cardiac” and “extra-cardiac” PMI was largely based on clinical criteria, as the majority of patients did not undergo coronary angiography.

Conclusion

PMI is a common complication following non-cardiac surgery and despite early detection during routine clinical screening 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 AMI versus those that do.

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Author contributions

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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Tables

Table 1 Baseline characteristics, shown for all cases and split for occurrence of Perioperative myocardial injuries (PMI), data shown as median [interquartile range limits] or counts (percentage); TIA = transient ischemic attack, RCRI = revised cardiac risk index; *comparisons were done using Mann-Whitney-U or Fisher's exact test as appropriate.

	All patients n = 2546	PMI n = 397	No PMI n = 2149	p-value*
Age – years	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
RCRI class II	814 (32%)	130 (33%)	684 (32%)	
RCRI class III	419 (16%)	91 (23%)	328 (15%)	
RCRI class VI	207 (8%)	66 (17%)	141 (7%)	
Elective surgery	1772 (70%)	242 (61%)	1530 (71%)	<0.001
Emergency surgery (≤24h)	314 (12%)	69 (17%)	245 (11%)	
Urgent surgery (>24h)	460 (18%)	86 (22%)	374 (17%)	

Table 2 Clinical presentation, electrocardiographic (ECG) changes, and cardiac workup within seven days in patients experiencing a perioperative myocardial injury (PMI), shown also for different PMI subtypes; *rales, wheezing, or effusion; †pre and postoperative ECG available in 244 patients

	PMI n = 397	PMI - cardiac n = 342	PMI - non-cardiac 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 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%)

Table 3 Multivariate Cox proportional hazards model for 30-day and one-year-mortality after Perioperative myocardial injury (PMI), shown for models including PMI and including PMI split in cardiac and extra-cardiac subtype. Shown as hazard ratios (HR) with (95%CI); RCRI = revised cardiac risk index

Model with PMI	HR 30-day mortality	p-value	HR one-year mortality	p-value
PMI	2.73 (1.54-4.84)	0.001	1.58 (1.16-2.15)	0.003
Age – years	1.06 (1.03-1.10)	0.001	1.05 (1.04-1.07)	<0.001
Non-elective 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				
PMI – cardiac	2.28 (1.19-4.36)	0.013	1.48 (1.07-2.06)	0.019
PMI - non-cardiac	4.44 (1.85-10.63)	0.001	2.27 (1.20-4.27)	0.011
Age -years	1.07 (1.03-1.10)	<0.001	1.06 (1.04-1.07)	<0.001
Non-elective 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

Table 4 High-sensitivity cardiac troponin T (hs-cTnT) levels with interquartile range, number above the 99th percentile with percent and maximum perioperative delta shown for all patients, those with and without perioperative myocardial injury (PMI), as well as for subtypes cardiac and extra-cardiac PMI

	preoperative hs-cTnT - ng/L	preop values above 99th - n (%)	maximum postoperative hs-cTnT - ng/L	postop values above 99th - n (%)	maximum perioperative Δhs-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)
PMI - cardiac	27 (15-51)	262 (79)	58 (41-109)	342 (100)	24 (17-43)
PMI - extra-cardiac	45 (18-95)	42 (84)	114 (53-175)	55 (100)	33 (19-83)

Figures

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

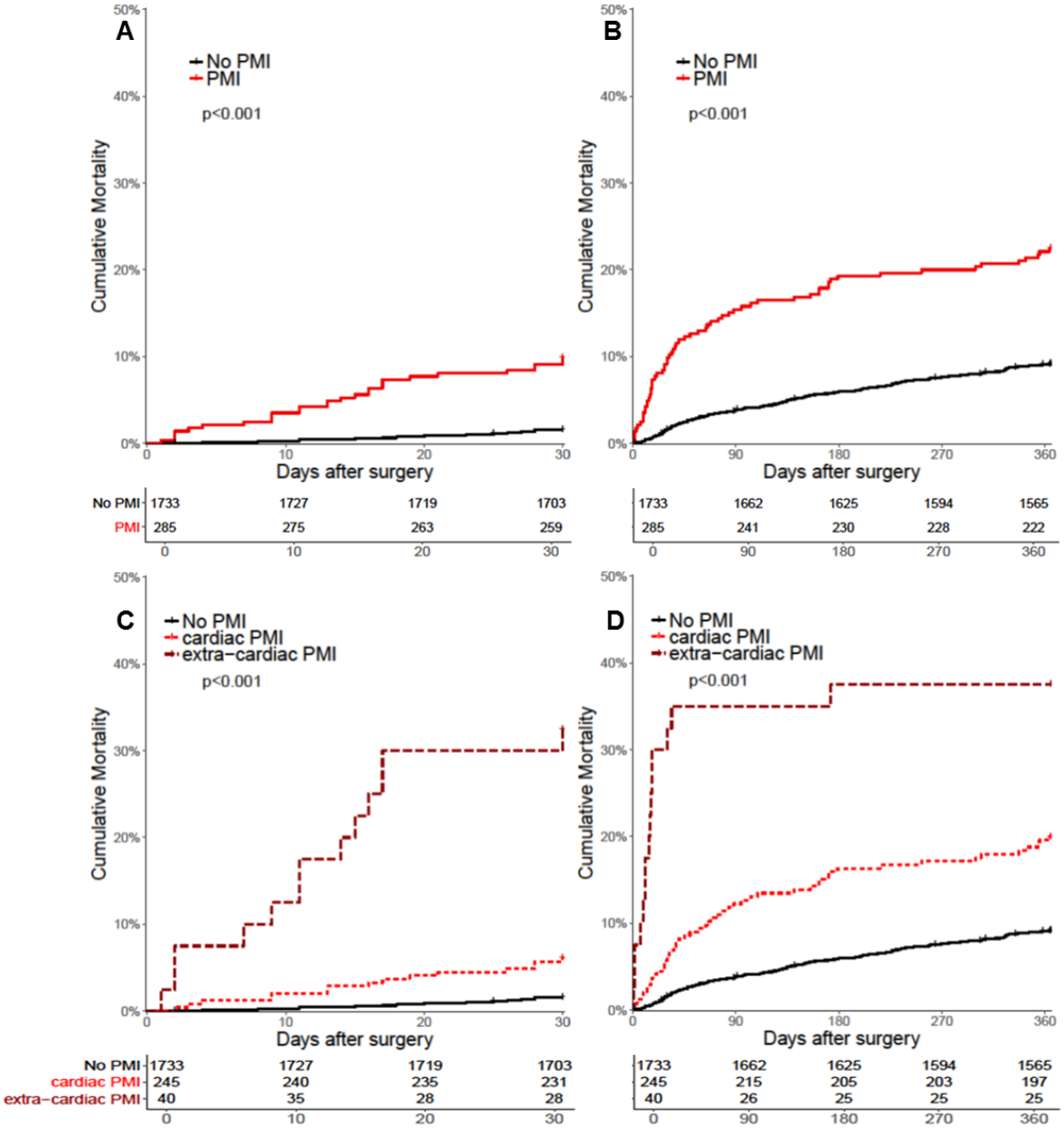


Figure 2 Cumulative all-cause mortality within 30-days and one-year of patients with perioperative myocardial injury (PMI), split according to whether patients not fulfilling any of the additional criteria required for the diagnosis of spontaneous acute myocardial infarction besides the cardiac troponin criterion (ischemic symptoms, or ischemic sings on electrocardiography or on cardiac imaging) or if they fulfill at least one of the additional criteria

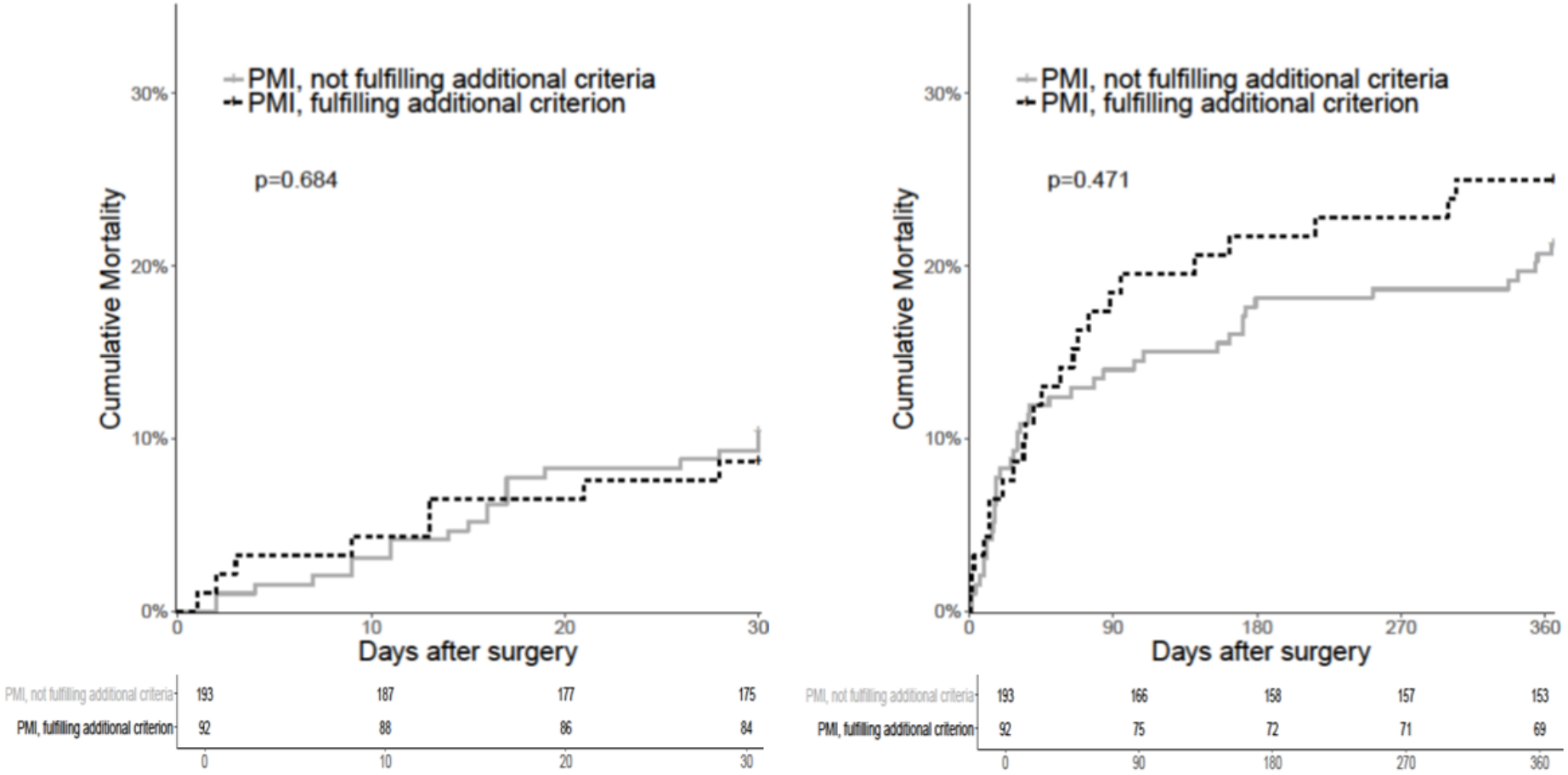


Figure 3 Association of absolute high-sensitivity cardiac troponin T (hs-cTnT) increase and maximum postoperative hs-cTnT level with 30-day mortality (black continuous line with 95%-confidence intervals in grey). A general linear fit is shown as red dashed line. As the association of absolute hs-cTnT increase with 30-day mortality might be affected by identifying and flagging PMI patients 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)

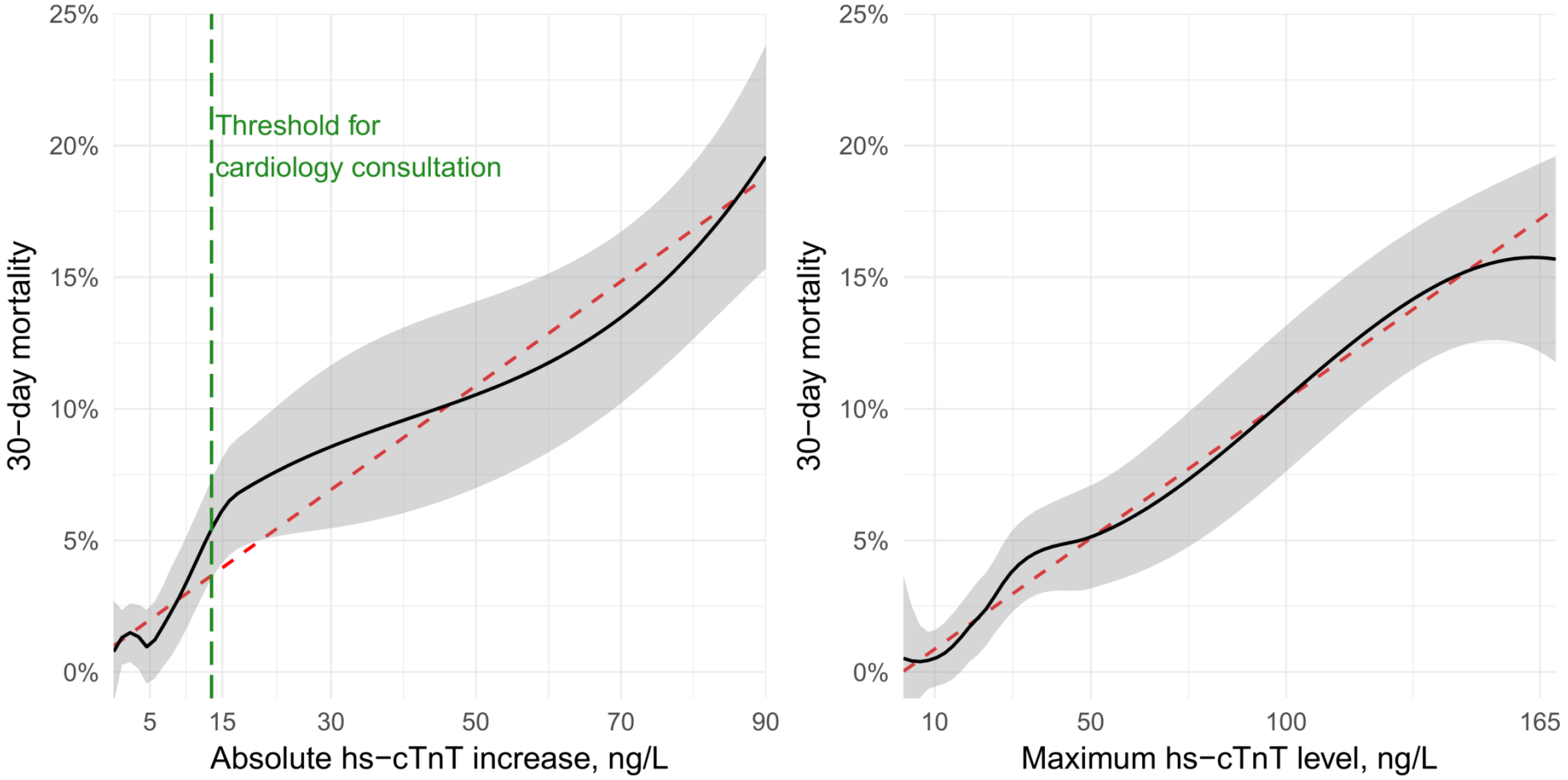
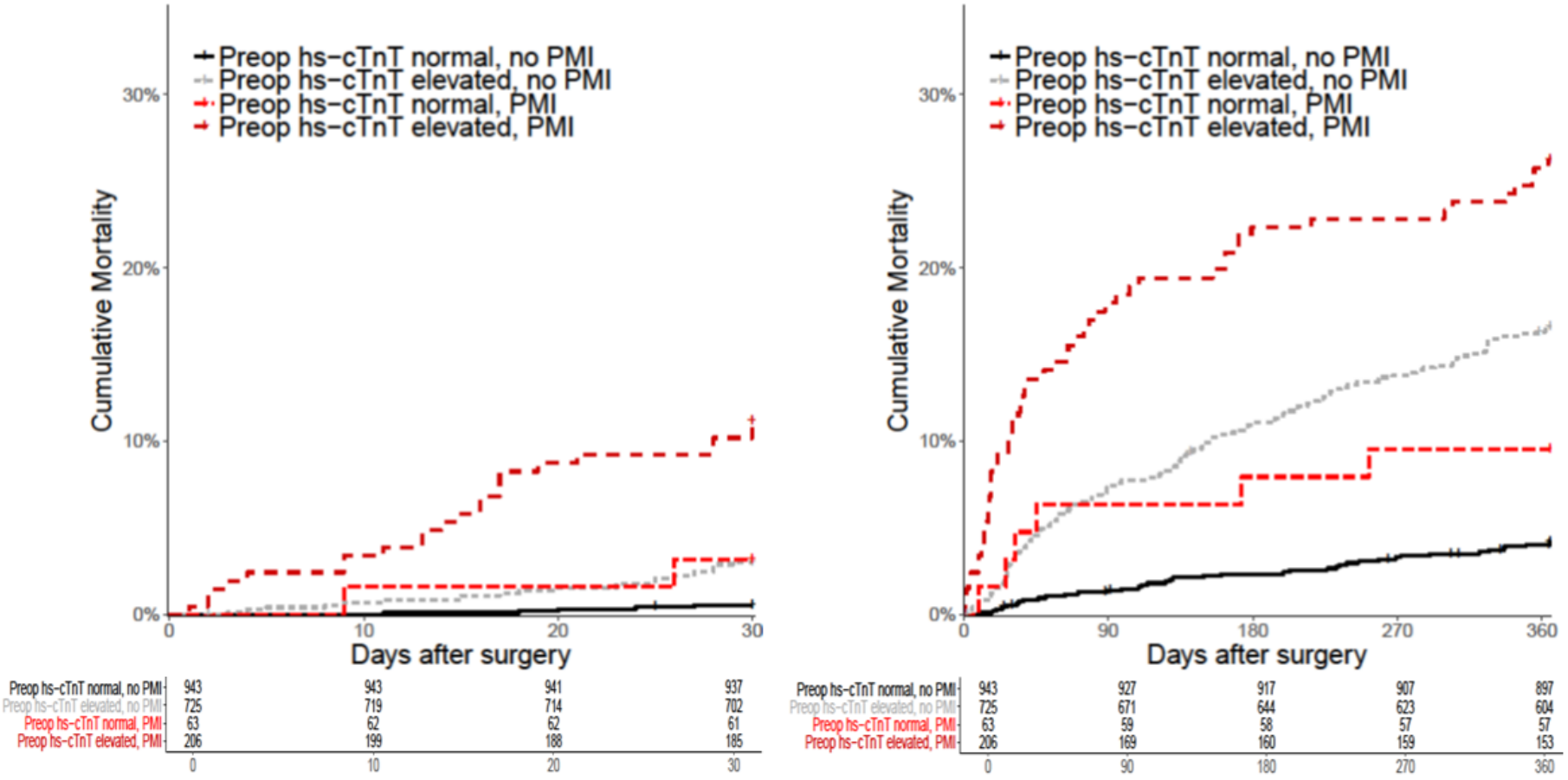


Figure 4 Cumulative all-cause mortality within 30-days and one year of all patients stratified according to preoperative high-sensitivity cardiac troponin T (hs-cTnT) levels (above or below the 99th percentile) and occurrence of perioperative myocardial injury (PMI) after surgery (n=1937)



Supplement

Outcome definitions

Further baseline definitions

Coronary artery disease was defined as history of coronary artery disease, history of acute myocardial infarction, finding of stenosis on coronary angiogram, or positive stress testing.

Peripheral artery disease was defined as history of peripheral artery disease, known carotid stenosis, or arterial vascular surgery for aortic aneurysm.

Stroke was defined as history of acute new focal neurological deficit judged by treating physicians to be of vascular cause lasting >24 hours

Chronic heart failure was defined as history of congestive heart failure, left ventricular ejection fraction ≤40%, or diastolic dysfunction grade II or higher with elevated B-type natriuretic peptide irrespective of ejection fraction.

Atrial fibrillation was defined as history of at least paroxysmal atrial fibrillation occurring more than once, or atrial fibrillation on preoperative ECG.

Complications

Sepsis was defined as clinical syndrome with presence of infection and clinical symptoms according to the International Sepsis Definitions Conference[66].

Stroke was defined as new focal neurological deficit judged by treating physicians to be of vascular cause lasting >24 hours.

Pneumonia was collected from discharge diagnosis. If sepsis criteria were fulfilled at diagnosis, sepsis was adjudicated instead.

Pulmonary embolism was collected from discharge diagnosis.

Postoperative delirium was defined as delirium with onset within 7 days after surgery, as extracted from medical charts

Supplement Tables

Supplement Table 1 Baseline characteristics of excluded patients compared to patients analysed. Data shown as median [interquartile range limits] or counts (percentage); TIA = transient ischemic attack, RCRI = revised cardiac risk index; *indicates significant differences compared to the cases analyzed assessed by Mann-Whitney-U or Fisher's exact test as appropriate

	Cases analyzed n = 2546	Only 1 hs-cTnT available n = 253	No preoperative hs-cTnT available and elevated post-op n = 48
Age - years	74 [68-79]	72 [66-77]*	76 [70-81]
Sex - male	1468 (58%)	147 (58%)	27 (56%)
Coronary artery disease	735 (29%)	85 (34%)	21 (44%)*
Prior myocardial infarction	378 (15%)	45 (18%)	9 (19%)
Chronic heart failure	322 (13%)	29 (12%)	5 (10%)
Atrial fibrillation	415 (16%)	35 (14%)	10 (21%)
Valuvlar heart disease	306 (12%)	28 (11%)	7 (15%)
Peripheral artery disease	475 (19%)	57 (23%)	5 (10%)
Prior stroke/TIA	254 (10%)	26 (10%)	7 (15%)
Hypertension	1694 (67%)	161 (64%)	30 (63%)
Diabetes mellitus	621 (24%)	75 (30%)	14 (29%)
Pneumopathy	408 (16%)	55 (22%)*	8 (17%)
Hepathopathy	166 (7%)	20 (8%)	2 (4%)
Active tumor disease	674 (26%)	67 (27%)	14 (29%)
RCRI class I	1106 (43%)	82 (33%)*	18 (38%)
RCRI class II	814 (32%)	97 (38%)	13 (27%)
RCRI class III	419 (16%)	47 (19%)	7 (15%)
RCRI class VI	207 (8%)	26 (10%)	10 (21%)
Elective surgery	1772 (70%)	137 (54%)*	35 (73%)
Emergency surgery (≤24h)	314 (12%)	59 (23%)	6 (13%)
Urgent surgery (>24h)	460 (18%)	56 (22%)	7 (15%)

Supplement Table 2 Incidence of perioperative myocardial injuries (PMI) shown according to surgical specialty as well as procedure related surgical risk category[25], data shown as percentage [95% confidence interval](absolute number of PMI/total cases group); ESC/ESA = European Society of Cardiology and the European Society of Anesthesiology

	Incidence of PMI [95%CI]	**ESC/ESA surgical risk**		
		<1%	1-5%	>5%
All surgical specialities	16% [14-17] (397/2546)	9% [9-13] (79/833)	17% [19-23] (248/1432)	25% [28-39] (70/281)
Orthopedic	16% [12-20] (50/315)	10% [6-18] (12/115)	20% [15-26] (36/183)	12% [2-36] (2/17)
Trauma	18% [15-22] (83/455)	12% [8-17] (22/188)	23% [19-29] (61/260)	0% [0-41] (0/7)
Spinal	15% [11-19] (55/372)	19% [6-44] (3/16)	15% [11-19] (52/356)	0% [0] (0/0)
Thoracic	24% [19-30] (53/219)	8% [0-38] (1/12)	22% [16-29] (38/174)	42% [27-59] (14/33)
Urologic	9% [6-12] (37/432)	6% [4-9] (19/319)	12% [7-19] (12/104)	67% [35-88] (6/9)
Vascular	20% [16-25] (66/322)	21% [12-33] (12/58)	15% [9-23] (14/96)	24% [18-31] (40/168)
Visceral	11% [8-15] (38/346)	6% [2-14] (5/84)	12% [9-17] (27/221)	15% [7-29] (6/41)
Other	19% [11-27] (15/85)	12% [5-26] (5/41)	21% [11-37] (8/38)	33% [10-70] (2/6)

Supplement Table 3 Details on surgical course and hospital stay of patients (n=2018) with and without perioperative myocardial injury (PMI), further shown for different subtypes of PMI. Data shown as median [interquartile range limits] or counts (percentage); ICU = intensive care unit

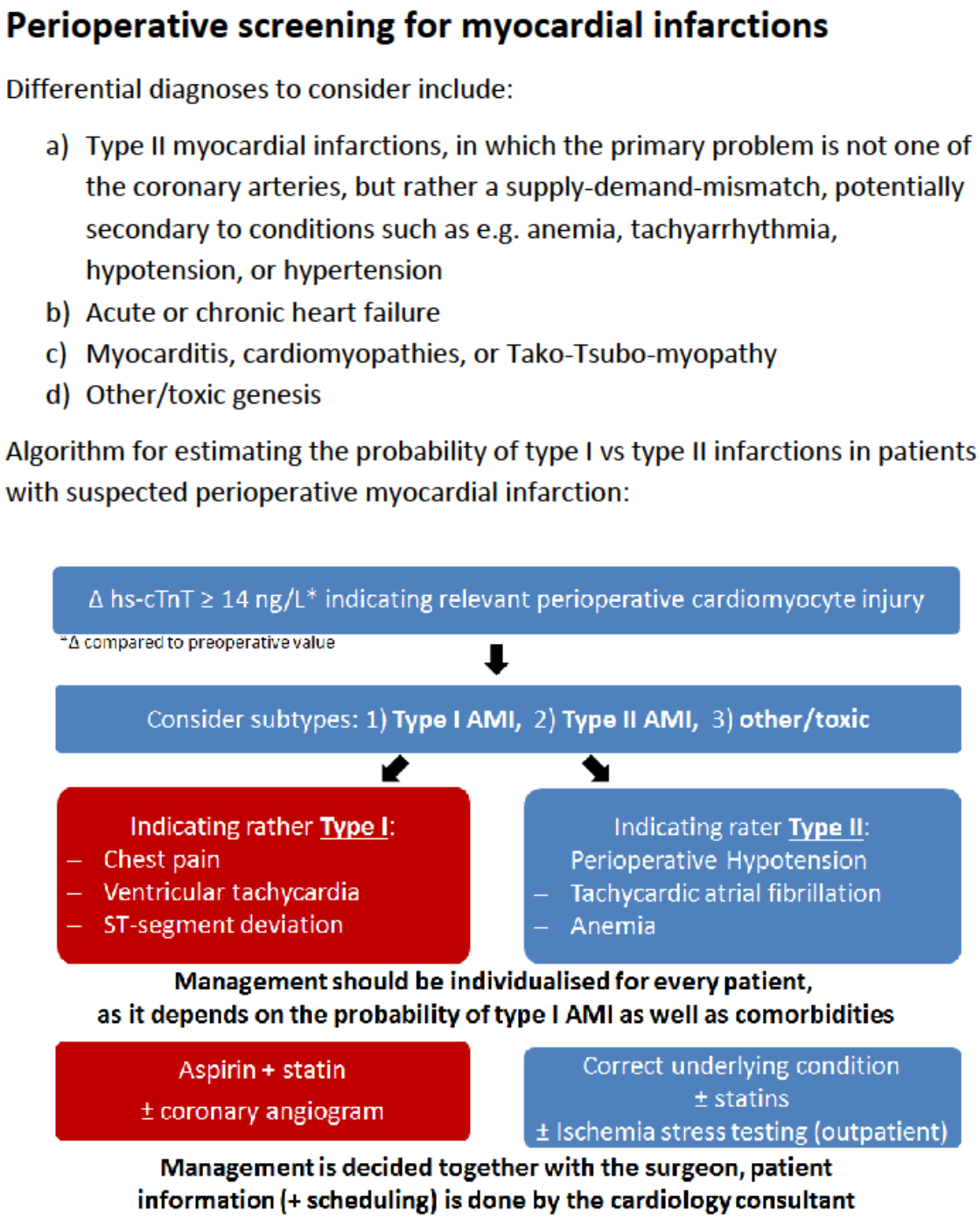
	No PMI n = 1733	PMI n = 285	PMI - cardiac n = 245	PMI - extra-cardiac n = 40
Surgery duration - min	117 [75-170]	150 [85-215]	153 [90-227]	120 [70-195]
ICU stay <2 days	220 (13%)	42 (15%)	34 (14%)	8 (20%)
ICU stay ≥2 days	35 (2%)	42 (15%)	24 (10%)	18 (45%)
Blood transfusion on day of surgery	73 (4%)	57 (20%)	44 (18%)	13 (33%)
Blood transfusion <postop day 2	93 (5%)	69 (24%)	60 (24%)	9 (23%)
Blood transfusion ≥postop day 2	299 (17%)	108 (38%)	87 (36%)	21 (53%)
Complications during hospital stay				
Sepsis	46 (3%)	28 (10%)	9 (4%)	19 (48%)
Stroke	13 (1%)	10 (4%)	5 (2%)	5 (13%)
Pneumonia	43 (2%)	30 (11%)	21 (9%)	9 (23%)
Pulmonary embolism	7 (0%)	7 (2%)	3 (1%)	4 (10%)
Postoperative delirium	46 (3%)	34 (12%)	27 (11%)	7 (18%)
Length of hospital stay - days	7 [4-10]	12 [8-18]	11 [8-17]	17 [9.5-24]

Supplement Table 4 Details on number of cardiology consultations, cardiac imaging, and changes in cardiovascular medication done in patients with and without perioperative myocardial injury (PMI) detected by routine screening. *for patients alive at discharge (n=2488)

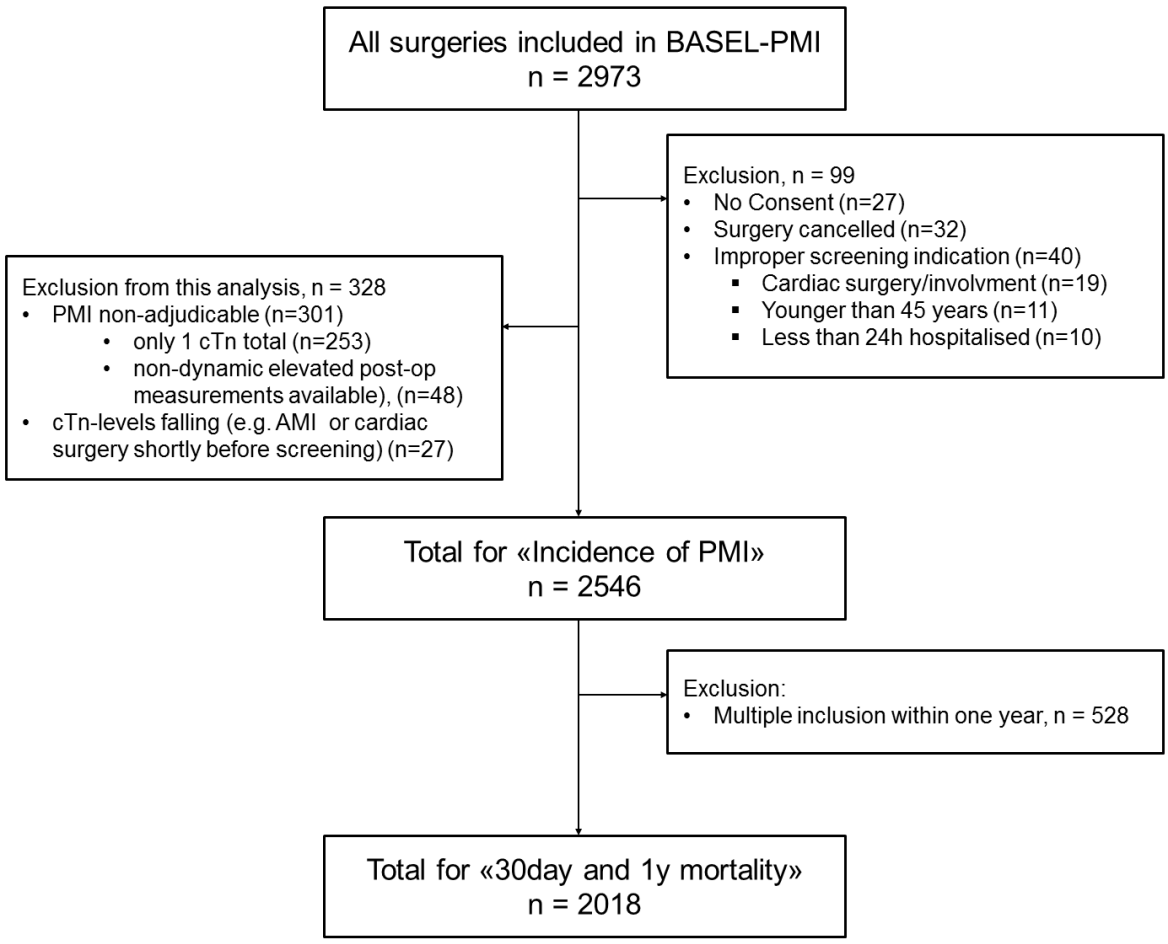
	PMI n = 397	No PMI n = 2149
Postoperative cardiology consultation	206 (52%)	64 (3%)
Cardiac workup within 30 days		
Coronary angiography	31 (8%)	11 (1%)
Myocardial perfusion imaging	11 (3%)	6 (0%)
Echocardiography	88 (22%)	93 (4%)
New cardiovascular medication at discharge*		
Any of the below	105 (29%)	263 (12%)
Acetyl salicylic acid	36 (10%)	48 (2%)
P2Y12 inhibitors	20 (5%)	20 (1%)
Statins	35 (10%)	34 (2%)
Betablockers	30 (8%)	57 (3%)
Renin-angiotensin-aldosteron-system inhibitors	32 (9%)	104 (5%)
Calcium channel blockers	17 (5%)	81 (4%)

Supplemental Figures

Supplemental Figure 1 Predefined management scheme for cardiologists at the University Hospital Basel providing cardiology consultations following perioperative myocardial injuries (PMI), translated from German. All treatment decisions regarding PMI were made by the treating surgeon in conjunction with the consulting cardiologist



Supplement Figure 2 Study population selection. Patients could be included multiple times into the study, but where only considered at their first surgery for prognostic analyses; PMI = perioperative myocardial injury; cTn = cardiac troponin; AMI = acute myocardial infarction



II Prediction of major cardiac events after vascular surgery

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Abstract

Objective: Predicting cardiac events is essential to provide patients best medical care and to assess the risk-benefit-ratio of surgical procedures. The aim of our study was to evaluate the performance of the Revised Cardiac Risk Index (Lee) and the Vascular Study Group of New England Cardiac Risk Index (VSG) scores for the prediction of major cardiac events in unselected patients undergoing arterial surgery and to determine if the inclusion of additional risk factors improved their accuracy.

Methods: 954 consecutive patients undergoing arterial vascular surgery were prospectively enrolled and Lee and VSG scores were calculated. Receiver Operating Characteristic curves for each cardiac risk score were constructed and the areas under the curve (AUC) compared. Two logistic regression models were done to determine new variables related to the occurrence of major cardiac events (myocardial infarction, heart failure, arrhythmias and cardiac arrest).

Results: Cardiac events occurred in 120 (12.6%) patients. Both scores underestimated the rate of cardiac events across all risk strata. The VSG score had AUC of 0.63 (95%CI, 0.58-0.68), which was higher than the AUC of the Lee score (0.58; 95%CI, 0.52-0.63; P=.03). Addition of preoperative anaemia significantly improved the accuracy of the Lee score to an AUC of 0.61 (95%CI, 0.58-0.67; P=.002), but not that of the VSG score.

Conclusions: The Lee and VSG scores have low accuracy and underestimate the risk of major perioperative cardiac events in unselected patients undergoing vascular surgery. Lee score´s accuracy can be increased adding preoperative anemia. Underestimation of major cardiac complications may lead to incorrect risk-benefit assessments regarding the planned operation.

Introduction

More than 300 million major surgeries are performed annually worldwide[2]. Patients submitted to arterial vascular surgery have an especially high risk of cardiac complications due to a high concomitant prevalence of atherosclerosis[67,68]. Cardiac events including myocardial infarction (MI), acute heart failure (AHF), and major arrhythmias after vascular surgery are a major concern for physicians and patients as they are associated with an increase in mortality, length of stay and cost[11,69]. Therefore, predicting cardiac events is essential to provide patients best medical care and also to assess the risk-benefit-ratio of surgical procedures.

Although the use of clinical risk scores to predict postoperative cardiac events is recommended by most guidelines[25,26,70], there is no specific recommendation for patients undergoing arterial vascular surgery. The Revised Cardiac Risk Index, developed by Lee et al (Lee score)[35] is widely used to estimate cardiac risk for different procedures, but may underestimate risk in patients submitted to arterial vascular surgery[71]. The Vascular Study Group of New England Cardiac Risk Index (VSG) is a dedicated score to predict cardiac risk in patients submitted to vascular surgery, specifically developed for this population[72]. Lee and VSG scores were developed in selected populations, ie. undergoing elective surgery and specific types of procedures. Their accuracy in real-world unselected patients undergoing vascular surgery is largely unknown.

The aim of our study was to evaluate the performance of the Lee and the VSG scores for the prediction of major cardiac events in unselected patients undergoing arterial surgery. Our secondary aim was to determine if the inclusion of additional risk factors improves their accuracy.

Methods

Study design and overview

The GREAT (Global Research on Acute Conditions Team) Perioperative Initiative is an ongoing prospective international collaboration aiming to improve cardiovascular perioperative care. For this analysis, individual patient data from two prospective cohorts were pooled: 1) from September 2012 to March 2016, we included consecutive patients undergoing arterial vascular surgery at the Clinics Hospital, University of São Paulo Medical School, Brazil, for whom a preoperative cardiologic consultation was requested. In São Paulo there is a special routine for patients undergoing arterial surgery, in which patients are systematically seen by cardiologists before surgery. 2) from October 2014 until October 2015, consecutive patients undergoing vascular surgery at Basel University Hospital, Switzerland were included. The University Hospital of Basel implements a perioperative troponin screening in clinical routine since October 2014 in patients at high perioperative cardiovascular risk undergoing major non-cardiac surgery. All screened patients are registered in a dedicated prospective database. The protocol was approved by the local ethics committees and informed consent was not required.

Patients

We included patients undergoing all vascular arterial surgeries: open or endovascular (for aorta, peripheral artery, visceral arteries and carotid artery diseases and amputations due to limb ischemia), emergent, urgent or elective. Patients who were not submitted to arterial surgery or patients who underwent renal transplantation were excluded (Supplement Figure I in the supplemental content)

Preoperative assessment and scores

Patients were submitted to clinical evaluation, and Lee[35] and VSG[72] scores were applied (Figures I and II). The Lee score is routinely used for preoperative evaluation in clinical practice and was taken into account by the attending physician to guide perioperative management according to local guidelines[25,26]. Preoperative additional cardiac tests were done at discretion of the attending physician, following local guidelines[25,26].

Previous coronary artery disease (CAD) was considered if the patient had history of myocardial infarction (MI), angina pectoris or myocardial revascularization (CABG or PCI), or evidence of CAD in myocardial perfusion imaging (presence of fixed or reversible perfusion defects) or coronary angiography. Preoperative chronic heart failure (CHF) was considered if there were: clinical symptoms consistent with CHF regardless of left ventricle ejection fraction (LVEF), LVEF lower than 50% assessed by echocardiography or LVEF lower than

45% assessed by GATED SPECT obtained during myocardial perfusion imaging. In cases with diagnostic uncertainty, BNP or NT-proBNP levels were used if available. In patients with CHF diagnosis, NYHA functional class was obtained by cardiologists. Smoking status included current and prior smokers. Anaemia was diagnosed according to World Health Organization (WHO) criteria as hemoglobin levels below 12g/dl for women and below 13g/dl for men[73].

Perioperative Surveillance

Perioperative surveillance included serial measurements of high-sensitivity cardiac Troponin T (hs-cTnT; Roche Diagnostics) once daily up to the second or third day after surgery, and 12-lead electrocardiogram (ECG) daily in São Paulo and in case of hs-cTnT elevations in Basel. Additional ECG and hs-TnT measurements were performed whenever clinically indicated. Hs-cTnT was selected due to its improved diagnostic accuracy compared to other less sensitive cTn assays in the diagnosis of MI[23]. Patients were followed-up until hospital discharge.

Clinical endpoints

The primary endpoint was a composite of cardiac events, including perioperative myocardial infarction (MI), acute heart failure (AHF), clinically relevant arrhythmias and cardiac arrest until hospital discharge. All endpoints were adjudicated by two cardiologists. MI was diagnosed according to the Third Universal Definition of Myocardial Infarction[17]. AHF was diagnosed by the attending physician, by clinical symptoms, physical examination, chest x-ray,BNP or NT-proBNP blood concentrations, and echocardiography[74]. Arrhythmias (atrial fibrillation/flutter, supraventricular tachycardia, ventricular tachycardia) were considered clinically significant if requiring drug therapy or electrical cardioversion. We chose this combined endpoint because it is the same endpoint used in the derivation of the Lee and VSG scores[35,72].

Statistical analysis

Categorical variables are presented as frequencies (percentages) and were compared by χ-square test or Fisher's test, as appropriate. Numerical variables are reported as medians and interquartile range (IQR) and were compared by Mann-Whitney test. We evaluated the incidence of the combined endpoint in each category of each cardiac risk score. Confidence intervals for incidence of the endpoint were calculated using the standard formula.

For our primary analysis, comparison of the risk scores, Receiver Operating Characteristic (ROC) curves for each cardiac risk score were constructed and the areas under the curve (AUC) compared by the method by DeLong[75]. Confidence intervals were constructed using

bootstrap. Sensitivity analysis for the AUC of both scores was done by excluding patients undergoing emergency or urgent surgeries. A post-hoc subgroup analysis of patients undergoing open or endovascular procedures was also performed.

For our secondary analysis, to determine new variables independently related to the occurrence of cardiac events after surgery, two binary logistic regression models for each score were created including the scores and variables preselected by literature research (urgency, anaemia, preoperative medication use)[25,26,35,38,70,72,76–79]. As power estimation for our regression analysis, we chose to include a maximum number of covariables of one variable per ten events[80]. The same variables were included in both models, except for variables that were already part of the respective score, such as “type of surgery” in Lee score or “smoking status” in VSG score. Variables with a p-value <0.05 were then added to the scores and ROC curves of the scores including the new variables were constructed. AUCs of the modified scores and of the original scores were compared.

P-values of less than 0.05 were considered to indicate statistical significance. Analyses were performed using SPSS 22 (IBM Co., NY, USA) and R software (Version 3.1.3, “pROC”[81]).

Results

One thousand two hundred and twenty-six patients were evaluated, and 272 were excluded (Supplement Figure I in the supplemental content). Baseline characteristics and outcome of patients divided by hospital are shown in Table I. Baseline characteristics of 954 patients included with and without a cardiac event are shown in Table II. About one-third of patients underwent aortic aneurism repair, one-third lower extremity bypass or angioplasty and one-fourth carotid procedures (Table III). Overall, 71% of patients underwent elective surgery, 24% urgent and 5% emergent (within one day) surgeries.

The primary endpoint of major cardiac events occurred in 120 (12.6%) patients. MI occurred in 66 (6.9%) patients, AHF in 46 (4.8%), clinically relevant arrhythmias in 24 (2.5%) and cardiac arrest in 13 (1.4%). The primary endpoint and MI incidence according to type of surgery is shown in Table III.

As for postoperative surveillance, 5% of patients did not have postoperative troponin values available. Median length of hospital stay was five days (IQR 3-8). Seventy-one patients died in-hospital, resulting in an in-hospital all-cause mortality rate of 7.4%.

Accuracy of established scores

The incidence of the primary endpoint according to risk strata for each cardiac risk score is shown in Table IV and Figure III. The observed risk was substantially higher than that predicted by both scores, particularly in the lower strata. Prognostic accuracy as quantified by the AUC was low for both scores. ROC curves for Lee (AUC 0.58; 95%CI, 0.52-0.63) and VSG scores (AUC 0.63; 95%CI, 0.58-0.68) are shown in Figure IV. Comparison of the two AUC showed the VSG score to be superior to the Lee score (p=0.03). Sensitivity analysis showed similar results when we analyzed only the 620 patients (78 events, 12.6%) submitted to elective surgery: AUC of Lee score was 0.58 (95%CI, 0.51-0.65) and for VSG score was 0.61 (95%CI, 0.55-0.67).

Subgroup analysis of the type of approach (endovascular *vs*. open) did not show different accuracy of the scores: in patients submitted to endovascular procedures, AUC for Lee score was 0.56 (95%CI, 0.48-0.65) and for the VSG score was 0.64 (95%CI, 0.56-0.72) and, in patients submitted to open procedures, AUC for Lee score was 0.59 (95%CI, 0.52-0.66) and for the VSG score was 0.62 (95%CI, 0.56–0.68).

Additional variables related to cardiac events

Independent risk factors for the primary endpoint in the Lee score model (Table V.A) were: smoking (OR 1.8 95%CI 1.1-3.1; P=.03), preoperative anaemia (OR 2.0 95%CI, 1.3-3.0; p=0.001) and the Lee score itself (OR 1.3 95%CI, 1.0-1.5; p=0.04). In the VSG score model

(Table V.B), besides the VSG score (OR 1.2 95%CI, 1.1-1.4; p<.001), only anaemia remained as an independent predictor of the primary endpoint (OR 1.9 95%CI, 1.3-2.9; p=0.002).

Adding anaemia improved the accuracy for prediction of primary endpoint only for the Lee score (Figure V): AUC for Lee score plus anaemia of 0.61 (95%CI 0.58-0.67; p=0.002 for comparison with original Lee score). This power-up effect was not significant for the VSG score: AUC for VSG plus anaemia was 0.65 (95%CI, 0.60-0.70; P=.10 for comparison with original VSG score). AUC of the Lee score plus anaemia and VSG score were similar (0.61 vs. 0.63, respectively; p=0.50). Adding smoking to the Lee score did not improved accuracy measured by AUC (AUC for Lee score plus smoking was 0.59; 95%CI, 0.54-0.65).

Discussion

In this collaborative prospective observational study, we aimed to evaluate the performance of two preoperative risk scores in unselected patients undergoing vascular surgery. We report three major findings. First, both scores substantially underestimated the rate of major cardiac events across all risk strata. Second, both scores had low accuracy in a real world setting of unselected patients undergoing vascular surgery, but VSG score provided better discrimination compared to Lee score. Third, addition of anaemia to the Lee score improved its accuracy and equalized it to VSG in this sample.

In a real world unselected population, both Lee and VSG scores substantially underestimate cardiac risk. This is of major concern, as underestimation of major cardiac complications including MI, AHF, cardiac arrest, major arrhythmias and cardiac death invariably leads to incorrect risk-benefit assessments by physicians and patients regarding the planned operation.

We have found a much higher overall cardiac event rate than observed in the derivation cohorts (12.6% vs 6.3% for VSG and 2-2.5% for Lee)[35,72]. Vascular patients have previously been shown to have a higher risk of cardiac complications[77], therefore it was expected that our overall cardiac event rate would be higher than Lee et al.'s original paper. However, the finding of much higher cardiac event rate than VSG cohort was unexpected. There are some possible explanations for this finding.

First, surveillance and diagnostic criteria of MI were different among studies. In our cohort, we performed routine surveillance with hs-cTnT measurements after surgery due to its diagnostic superiority as compared to less sensitive assays[23], which allowed us to identify the vast majority of MIs in the first days. As in more than 50% of cases MIs patients do not complain of chest pain[6,13], most MIs will be missed without routine screening[4]. In a recent registry that included 88,791 patients submitted to non-emergent vascular operations the overall incidence of MI was 1.6%[76]. Previous studies also reported lower overall procedure specific perioperative MI rates than ours, most likely due to better surveillance in our prospective study[38,78]. As there is no specific universal definition for MI after non-cardiac surgery, the difference in incidence of MI in several studies depends on the diagnostic criteria and the cTn assay used[17].

Second, differences between cohorts need to be considered, such as baseline characteristics of the included patients and type of surgery. Overall, our population was older and had a higher prevalence of known CAD and CHF, consistent with current daily clinical practice. Forty percent of VSG score´s original population had a Lee score below class II, whereas only 14% of our population had a Lee score below class II[72]. The type of surgery is

also a major issue. Our inclusion criteria were broader than those from the VSG cohort which just included non-emergent carotid endarterectomy, open or endovascular infra-renal abdominal aortic aneurysm repair and lower extremity bypass[72]. Half of VSG population was submitted to carotid endarterectomy, while only 24% of our population underwent carotid surgery[72]. If we compare the VSG's results only for open abdominal aortic aneurysm repair, their complication rate ranged from 19% to 22%, similar to ours (15%). Additionally, one third of our patients underwent urgent/emergent procedures, which are usually associated to higher complication rates.

Underestimation of cardiac risk has serious implications for clinical practice. The decision to proceed to surgery or not is based on the risk-benefit ratio. The benefit of elective surgery depends on the vascular disease's complication rate. The annual risk of abdominal aortic aneurysm (AAA) rupture depends on its diameter and ranges from 0.5-5% in AAAs between 4.0 to 4.9 cm, to 30-50% in AAAs with a diameter greater than or equal to 8.0 cm[82]. In patients with PAD and claudication, only 1 to 2 % will progress to critical limb ischemia in 5 years[83]. For patients with asymptomatic carotid stenosis, the absolute benefit in stroke prevention for revascularization is 1-2% per year[84]. Previous randomized trials comparing carotid endarterectomy with medical therapy were performed before improvements in medical therapy[85,86]. It has been suggested that intensive medical treatment has reduced the annual rate of stroke from 2-5% to 1%[87,88]. Awareness that, patients classified as intermediate risk by Lee or VSG, have cardiac event rates around 10% is extremely important for the decision of the best treatment choice (surgery vs. medical treatment)[26]. Other comorbidities that could compromise quality of life and may improve with surgery, such as chronic pain and poor mobility, also have to be taken into account in this decision. Nevertheless, knowledge of the rate of complications is important so that physicians and patients together make an informed decision to improve global patient care. For patients undergoing urgent or emergent surgery, cancelling or postponing surgery is not an option, but estimation of cardiac events rate can also add important clinical information. Indeed, the knowledge that cardiac risk in higher than predicted empowers the evaluating physician for suggesting measures to reduce risk, such as giving statins, referring the patient to the intensive care unit after surgery and recommending surveillance for improving diagnosis and treatment of cardiac events.

Unfortunately, both scores had low to moderate accuracy in our population of unselected patients submitted to vascular surgery. This finding may at least in part be explained by the fact that both scores do not take into account the intraoperative period. It is well known that intraoperative complications including hypotension and bleeding are associated with the development of postoperative major cardiac events including death[79,89]. Nevertheless, VSG

score had a better accuracy than Lee score to predict cardiac events, a finding that is in line with previous studies[71,72]. In addition, Lee score could not discriminate well between the patients classified in class II and III risk strata. As Lee score had been part of the routine clinical preoperative evaluation to guide management at the participating institutions[25,26], classifying a patient as Lee class ≥ III may have led to changes in perioperative clinical care that could have an impact on outcome.

We have shown that the presence of anaemia is a strong predictor for cardiac events. Several previous studies have demonstrated that preoperative anaemia is a predictor of short- and long-term mortality after non-cardiac surgery, including vascular surgery[90–96]. However, the evidence for preoperative anemia as a predictor of cardiac events after all types of vascular surgery is still limited. In a retrospective study including 360 patients undergoing peripheral arterial reconstructive surgery, Oshin et al reported that preoperative hemoglobin levels were related not only to mortality but also to cardiac events after surgery[97]. In a large retrospective study evaluating 31,857 elderly patients (> 65 years old) of the National Surgical Quality Improvement Program (NSQIP) database undergoing elective mostly open vascular procedures, Gupta et al have demonstrated that low preoperative hematocrit values were related to mortality and to perioperative MI or cardiac arrest within 30 days[96]. In our prospective study, not only did we confirm that preoperative anaemia (as defined by WHO criteria) is an independent predictor of cardiac events in patients undergoing open or endovascular vascular procedures, but also provide a way to use this information in clinical practice. Although VSG score alone had better accuracy than Lee score alone in our population, it was equivalent of Lee score plus anaemia. The Lee score is simpler to calculate than VSG score and it is the score recommended by most guidelines[25,26]. As haemoglobin is routinely measured prior to surgery, incorporation of this biomarker as a power-up in the Lee score is a simple and no cost way of improving cardiac risk prediction.

Limitations

Our study has some limitations. First, our patients came from two tertiary centers, where patients usually are referred to when they have a more severe vascular disease or important cardiac or non-cardiac comorbidities. In the University of São Paulo, we included patients for whom cardiac consultation was requested and, although it is common practice at our institution for vascular surgeons to request cardiac evaluation for all patients, we may have missed patients in the lower risk strata. Second, we did not evaluate the NSQIP[39], MICA (myocardial infarction/cardiac arrest)[38] and Vascular Quality Initiative (VQI)[76] risk scores that are more complex and accurate than Lee and VSG scores. These scores have to be done online or using mobile applications, and only evaluate risk of MI and cardiac death, both

factors limiting practical clinical use[38,39,76]. Currently, with improvement of surgical and anaesthetic techniques, patients undergoing non-cardiac surgery are increasingly older and have more comorbidities, therefore it is also important to estimate the risk of other common cardiac complications besides MI and cardiac arrest, such as AHF and arrhythmias.

All risk prediction scores have advantages and limitations. They also were tested in different populations, different surgical procedures and predict different outcomes. Nevertheless, their use is recommended by most guidelines[25,26,70]. It is up to the attending physician to be aware of their individual strengths and limitations and choose the most appropriate one, depending on clinical context. Using more than one risk score with different endpoints (VSG score plus NSQIP, for example), could be a good option to improve risk prediction and patient care. However, it is extremely important to be aware that the incidence of cardiac events is probably higher than predicted in order to make appropriate risk-benefit assessments regarding surgery.

Conclusion

The Lee and VSG scores have low accuracy and underestimate the risk of major perioperative cardiac events in unselected patients undergoing vascular surgery, which can at least partly be increased for Lee by the addition of preoperative anemia. Underestimation of major cardiac complications may lead to incorrect risk-benefit assessments by physicians and patients regarding the planned operation.

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Tables

Table I Baseline characteristics and outcome divided by hospital

	All Patients	**Sao Paulo cohort**	**Basel cohort**	**p value**
	n = 954	n = 743	n = 211	
Male gender, n(%)	687 (72)	540 (73)	147 (70)	0.39
Age (years), median (IQR)	70 (63-76)	68 (62-75)	74 (68-79)	<0.001
Diabetes, n (%)	324 (34)	261 (35)	63 (30)	0.15
Insulin, n (%)	111 (12)	82 (11)	29 (14)	0.28
Hypertension, n(%)	795 (83)	627 (84)	168 (80)	0.10
Active/former smoker, n (%)	725 (76)	564 (76)	161 (76)	0.90
CAD, n (%)	377 (40)	286 (39)	91 (43)	0.22
CABG/PCI, n (%)	175 (18)	138 (19)	37 (18)	0.73
PAD	954 (100)	743 (100)	211 (100)	-
CHF, n (%)	154 (16)	128 (17)	26 (12)	0.09
NYHA FC ≥ II[*]	54 (6)	54 (7)	NA	
Hx Stroke/TIA, n (%)	232 (24)	195 (26)	37 (18)	<0.001
COPD, n (%)	90 (9)	51 (7)	39 (19)	<0.001
Creatinine[†] (mg/dL), median (IQR)	1.1 (0.8-1.4)	1.1 (0.9-1.4)	1 (0.8-1.4)	0.008
CRF in dialysis, n (%)	32 (3.4)	25 (3)	7 (3)	0.97
Anaemia[‡], n (%)	393 (41)	275 (37)	118 (56)	<0.001
Haemoglobin[‡] (g/dL), median (IQR)	13 (12-14)	13.2 (11.9-14.3)	12.4 (10.3-14)	<0.001
Preoperative medications				
ASA[‡], n (%)	774 (81)	637 (86)	137 (65)	<0.001

Clopidogrel, n (%)	78 (8)	47 (6.3)	31 (15)	<0.001
Statins n (%)	845 (89)	713 (96)	132 (63)	<0.001
Betablockers, n (%)	516 (54)	409 (55)	107 (51)	0.27
ACEI or ARB, n (%)	556 (58)	425 (57)	131 (62)	0.20
Preoperative cardiac assessment				
Myocardial perfusion imaging, n (%)	375 (39)	355 (48)	20 (10)	<0.001
Normal perfusion, n (%)	201 (21)	201 (27)	0	
Fixed perfusion defects, n (%)	104 (11)	100 (14)	4 (2)	<0.001
Reversible perfusion defects, n (%)	70 (7)	54 (7)	16 (8)	
Coronary angiography, n (%)	67 (9)	39 (5)	28 (13)	<0.001
TT echocardiography, n (%)	392 (41)	392(53)	NA	NA
Wall motion Abnormalities, n (%)	96 (10)	96 (13)	NA	NA
Primary endpoint	120 (12.6)	102 (13.7)	18 (8.5)	0.045

*n= 743; †n=952; ‡n=953; CAD = coronary artery disease; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; PAD = Peripheral artery disease CHF = chronic heart failure; NYHA FC = New York Heart association functional class Hx = previous history; TIA = Transient ischemic attack COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; ASA = aspirin; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; IQR= interquartile range; TT = Transthoracic; NA = not available.

Table II Clinical characteristics of all patients with and without cardiac events

	All Patients	**No cardiac events**	**Cardiac events**	**p-value**
	n = 954	n = 834	n = 120	
Male gender, n (%)	687 (72)	604 (72)	83 (69)	.46
Age (years), median (IQR)	70 (63-76)	69 (63-75)	71 (63-78)	.04
Diabetes, n (%)	324 (34)	277 (33)	47 (39)	.20
Insulin, n (%)	111 (12)	93 (11)	18 (15)	.35
Hypertension, n (%)	795 (83)	687 (82)	108 (90)	.04
Active/former smoker, n (%)	725 (76)	626 (75)	99 (82.5)	.07
CAD, n (%)	377 (40)	313 (38)	64 (53)	.001
CABG/PCI, n (%)	175 (18)	140 (17)	35 (29)	.001
PAD	954 (100)	-	-	
CHF, n (%)	154 (16)	121 (15)	33 (28)	< .001
NYHA FC ≥ II[a]	54 (8)	34 (5)	20 (20)	.02
Hx Stroke/TIA, n (%)	232 (24)	204 (25)	28 (23)	.79
COPD, n (%)	90 (9)	79 (10)	11 (9)	.92
Creatinine[b] (mg/dL), median (IQR)	1.1 (0.8-1.4)	1.1 (0.8-1.4)	1.2 (1.0-1.5)	.004
CRF in dialysis, n (%)	32 (3.4)	29 (4)	3 (3)	.79
Anaemia[c], n (%)	393 (41)	323 (39)	70 (58)	< .001
Haemoglobin[c] (g/dL), median (IQR)	13 (12-14)	13 (12-14)	12 (11-14)	< .001
Preoperative medications				
ASA[c], n (%)	774 (81)	669 (80)	105 (88)	.06
Clopidogrel, n (%)	78 (8)	72 (9)	6 (5)	.17
Statins n (%)	845 (89)	734 (88)	111 (93)	.15
Betablockers, n (%)	516 (54)	441 (53)	75 (63)	.05
ACEI or ARB, n (%)	556 (58)	481 (58)	75 (63)	.32

Preoperative cardiac assessment				
Myocardial perfusion imaging, n (%)	375 (39)	327(39)	48 (40)	.89
Normal perfusion, n (%)	201 (21)	176 (21)	25 (21)	
Fixed perfusion defects, n (%)	104 (11)	87 (10)	17 (14)	.50
Reversible perfusion defects, n (%)	70 (7)	64 (8)	6 (3)	
Coronary angiography, n (%)	67 (9)	59 (9)	8 (8)	.72
TT echocardiography, n (%)	392 (41)	320 (38)	72 (60)	NA
Wall motion Abnormalities, n (%)	96 (10)	70 (8)	26 (22)	

[a]n= 743; [b]n=952; [c]n=953; CAD = coronary artery disease; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; PAD = Peripheral artery disease CHF = chronic heart failure; NYHA FC = New York Heart association functional class Hx = previous history; TIA = Transient ischemic attack COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; ASA = aspirin; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; IQR = interquartile range; TT = Transthoracic

Table III Observed primary endpoint and perioperative MI according to type of surgery

Type of Surgery	**All Patients** n (%)	**Cardiac events** n (%)	**Perioperative MI** n (%)
Open aortic aneurysm repair	107 (11.2)	16 (15.0)	10 (9.3)
Endovascular aortic aneurysm repair	200 (21.0)	32 (16.0)	11 (5.5)
Lower extremity bypass	219 (23.0)	33 (15.1)	23 (10.5)
Lower extremity angioplasty	109 (11.4)	14 (12.8)	5 (4.6)
Carotid endarterectomy	151 (15.8)	15 (9.9)	12 (7.9)
Carotid stenting	82 (8.6)	3 (3.7)	2 (2.4)
Amputations	37 (3.9)	5 (13.5)	2 (5.4)
Others	49 (5.1)	2 (4.1)	1 (2.0)

MI = myocardial infarction

Table IV Observed primary endpoint according to risk strata for each cardiac risk score and predicted Risk

Cardiac Risk Scores	All Patients n (%)	Observed Cardiac events n (%, 95%-CI)	Predicted Risk (%)
Lee Score			
I	139 (14.6)	11 (**8**, 4-12)	(0.4)
II	337 (35.3)	39 (**12**, 8-15)	(0.9)
III	285 (29.9)	33 (**12**, 8-15)	(6.6)
IV	193 (20.2)	37 (**19**, 14-25)	(11.0)
VSG			
0-3	237 (24.8)	11 (**5**, 2-7)	(2.6)
4	181(19.0)	15 (**8**, 4-12)	(3.5)
5	166 (17.4)	31 (**18**, 13-25)	(6.0)
6	124 (13.0)	21 (**16**, 10-23)	(6.6)
7	98 (10.3)	15 (**15**, 8-22)	(8.9)
>8	148 (15.5)	27 (**18**, 12-24)	(14.3)

Lee RCRI = Revised Cardiac Risk Index by Lee; VSG = Vascular Study Group of New England Cardiac Risk Index

Table V Logistic regression models for prediction of primary outcome including Lee score (A) and VSG score (B)

A) Lee score	**OR**	**95%CI**	**p-value**
Age	1.2	1.0 - 1.4	0.066
Female sex	1.4	0.9 - 2.2	0.137
Hypertension	1.5	0.7 - 2.9	0.283
Urgency/emergency	1.4	0.9 - 2.1	0.158
Smoking	**1.8**	**1.1 - 3.1**	**0.026**
COPD	0.8	0.4 - 1.7	0.610
ASA	1.6	0.9 - 3.0	0.102
statins	1.3	0.6 - 2.9	0.450
betablockers	1.2	0.8 - 1.9	0.303
ACEI or ARB	1.1	0.7 - 1.6	0.756
Lee Score	**1.3**	**1.0 - 1.5**	**0.041**
Anemia	**2.0**	**1.3 - 3.0**	**0.001**
B) VSG score	**OR**	**95%CI**	**p-value**
Female sex	1.3	0.9 - 2.1	0.195
Hypertension	1.5	0.8 - 3.0	0.213
Urgency/emergency	1.3	0.8 - 2.1	0.236
Supra-inguinal surgery	1.1	0.7 - 1.8	0.616
Stroke/TIA	0.9	0.5 - 1.4	0.607
ASA	1.7	0.9 - 3.0	0.088
statins	1.5	0.7 - 3.2	0.299
ACEI or ARB	1.1	0.7 - 1.6	0.770
VSG score	**1.2**	**1.1 - 1.4**	**< 0.001**
	1.9	**1.3 - 2.9**	**0.002**

Anemia

OR = odds ratio; COPD = chronic obstructive pulmonary disease; TIA = Transient ischemic attack; ASA = aspirin; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers

Figures

Figure I Revised Cardiac Risk Index by Lee[35]

Revised Cardiac Risk Index (RCRI) by Lee

- ✓ **High-risk surgery (intra-thoracic, intra-peritoneal or suprainguinal vascular surgery)**
- ✓ **Coronary artery disease**
- ✓ **Chronic heart failure**
- ✓ **Cerebrovascular disease**
- ✓ **Diabetes on insulin**
- ✓ **Creatinine levels > 2.0mg/dL**

Class	Points	Predicted Cardiac Events (%)
I	0	0.4
II	1	0.9
III	2	6.6
IV	≥ 3	11

Figure II Vascular Study Group of New England Cardiac Risk Index (VSG)[72]

Vascular Study Group of New England Cardiac Risk Index (VSG)

Age ≥ 80 anos	**4 pts**	**Creatinine > 1.8 mg/dL**	**2 pts**
Age 70-79 anos	**3 pts**	**Current or previous smoking**	**1 pt**
Age 60-69 anos	**2 pts**	**Diabetes on insulin**	**1 pt**
Coronary artery disease	**2 pts**	**Chronic use of β-blockers**	**1 pt**
Chronic heart failure	**2 pts**	**Previous CABG or PCI**	**-1pt**
COPD	**2 pts**		

Points	Predicted Cardiac Events (%)
0 – 3	2.6
4	3.5
5	6
6	6.6
7	8.9
≥8	14.3

COPD = chronic obstructive pulmonary disease; CABG = coronary artery bypass graft surgery; PCI = coronary percutaneous intervention; pt = point

Figure III Combined endpoint according to risk strata for the Lee score (left) and the VSG (right), predicted event rate (green) vs observed event rate (red)

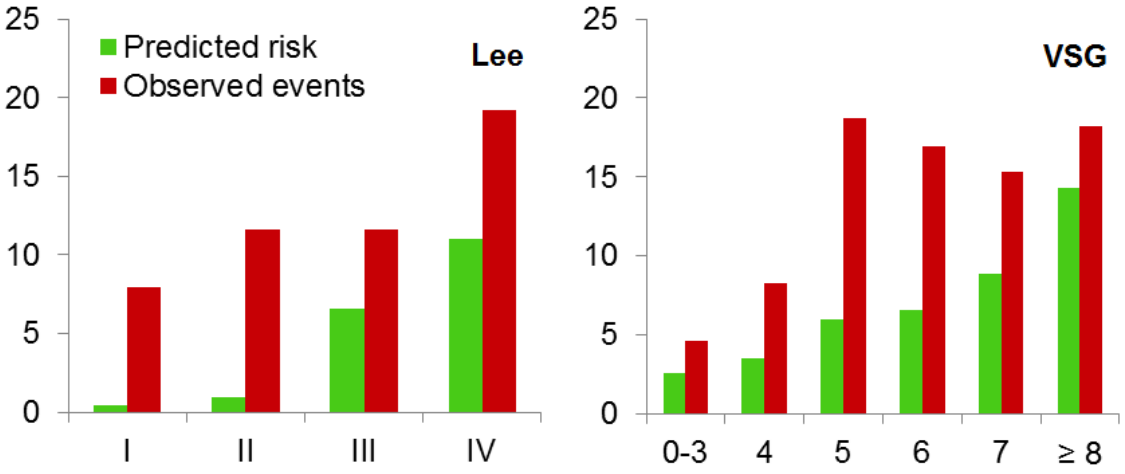


Figure IV Receiver operating characteristics curves of Lee (red) vs VSG (green) risk scores with 95% confidence intervals for sensitivity

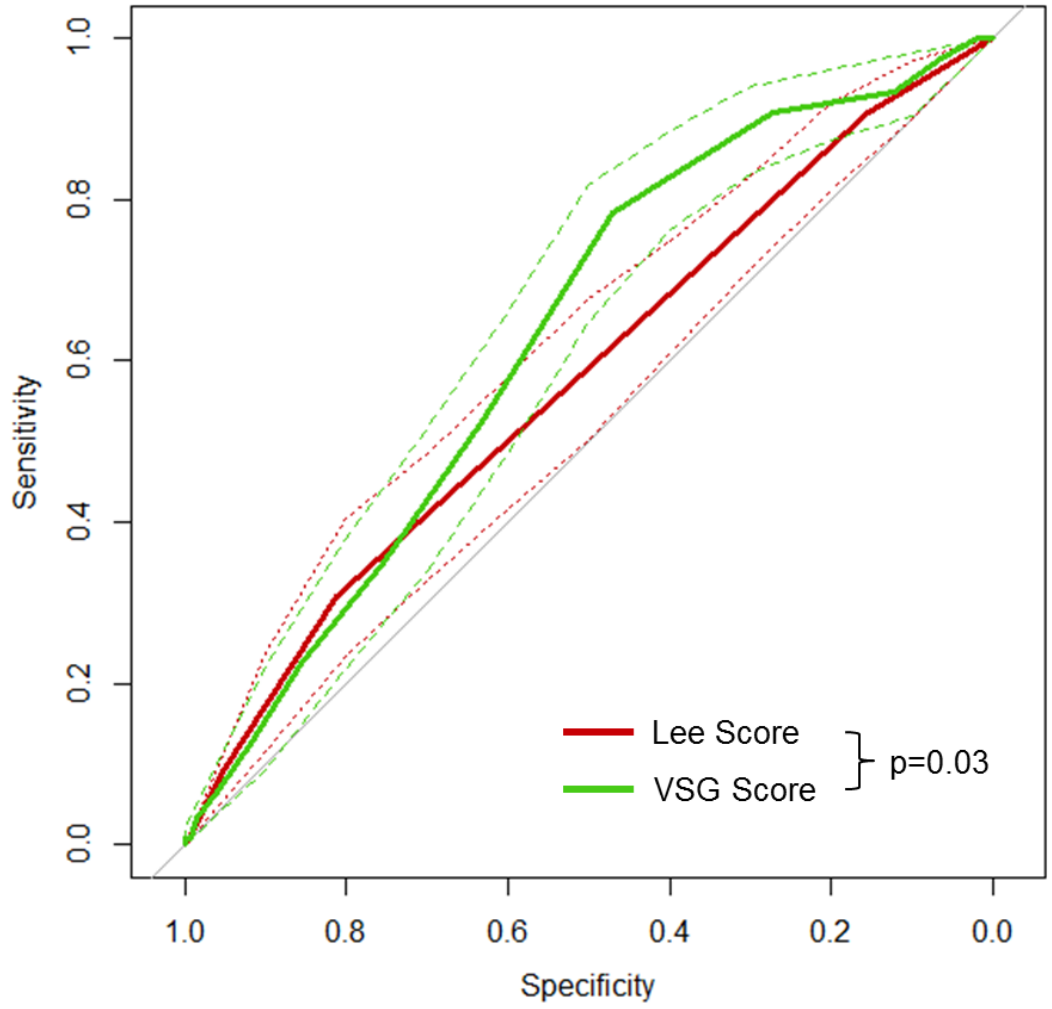
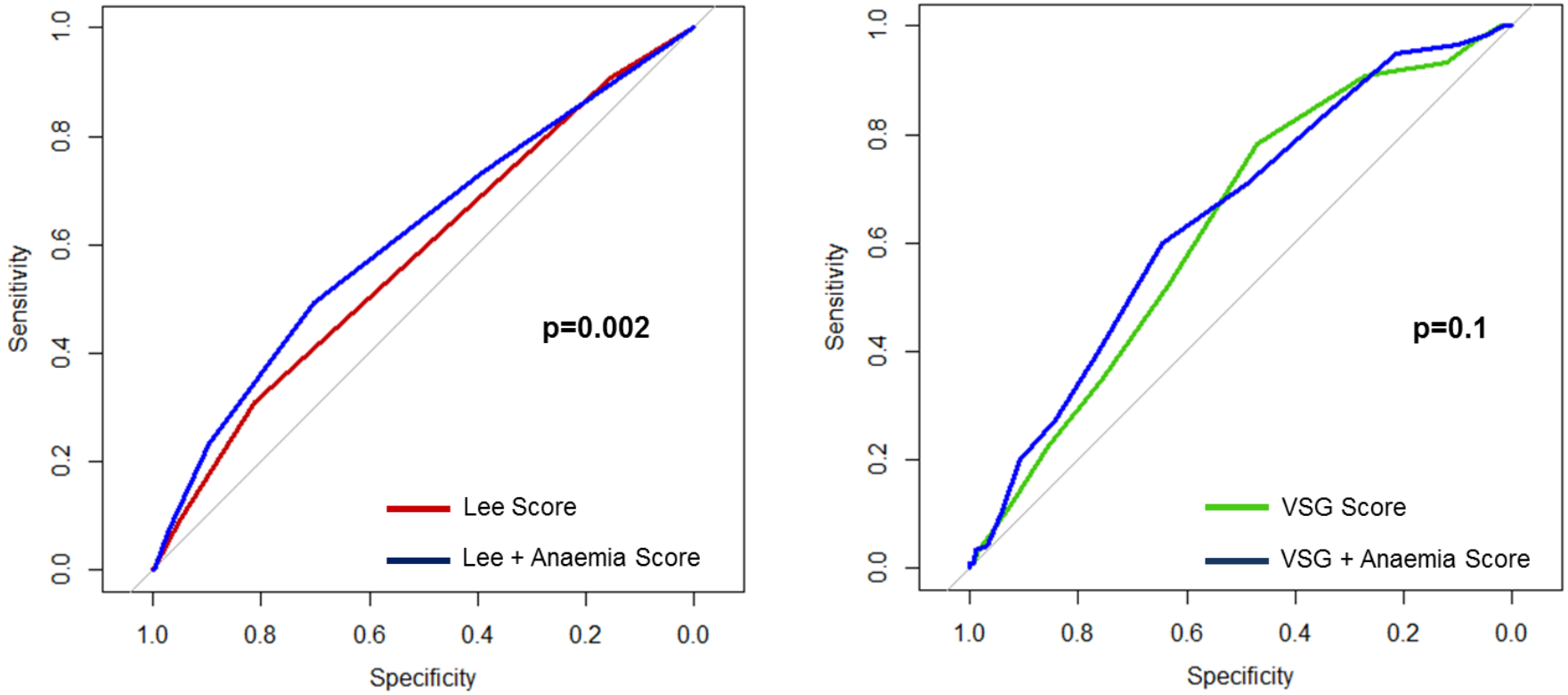
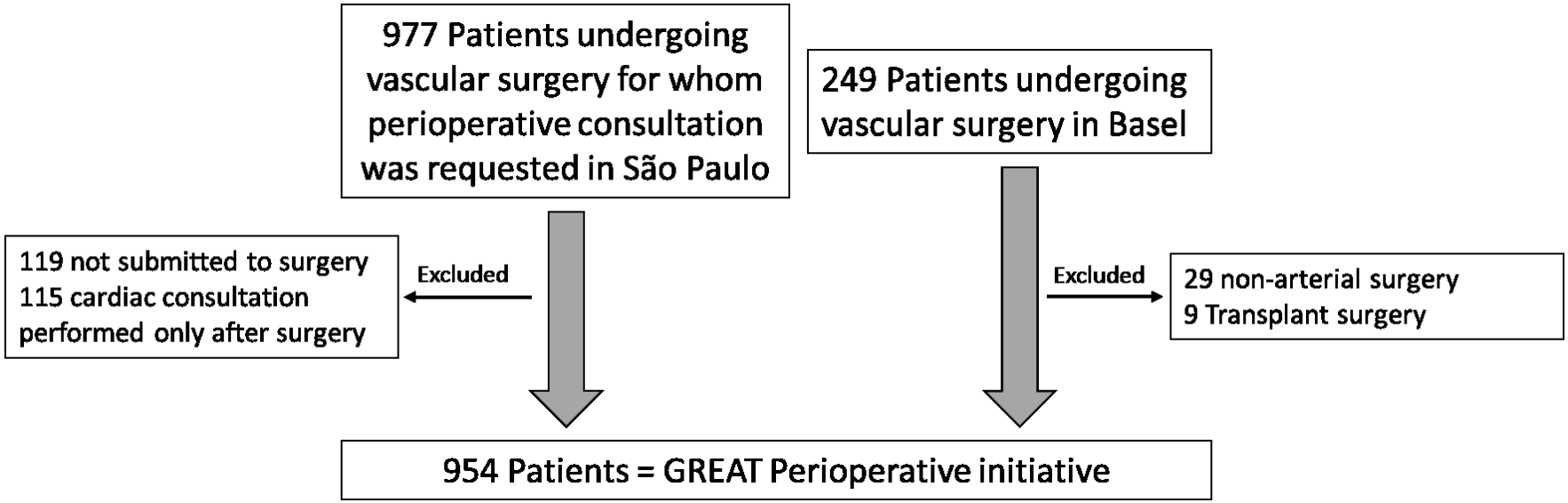


Figure V Receiver operating characteristics curves of Lee score (red) vs Lee score plus anaemia (blue, panel left) and VSG (green) score vs. VSG score plus anaemia (blue, panel right)



Supplement

Supplement Figure I Patient Flowchart



III Comparison of high-sensitivity cardiac troponin I and T for the prediction of cardiac complications after non-cardiac surgery

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Abstract

Aims: Predicting cardiac complications after non-cardiac surgery is challenging. We aimed to compare the accuracy of preoperative high-sensitivity cardiac troponin (hs-cTn) I and T concentration for the prediction of major cardiac complications after non-cardiac surgery.

Methods: We measured hs-cTnI and hs-cTnT preoperatively in a blinded fashion in 1022 consecutive patients undergoing non-cardiac surgery. The primary endpoint was a composite of major cardiac complications including cardiac death, cardiac arrest, myocardial infarction, clinically relevant arrhythmias, and acute heart failure within 30 days. We hypothesized that the type of surgery may impact on the predictive accuracy of hs-cTnI/T and stratified all analyses according to the type of surgery.

Results: Major cardiac complications occurred in 108 (11%) patients, 58/243 (24%) patients undergoing vascular surgery and 50/779 (6%, p<0.001) patients undergoing non-vascular surgery. Among patients undergoing vascular surgery, preoperative hs-cTnI, but not hs-cTnT, was an independent predictor of major cardiac complications (adjusted odds ratio (aOR) 1.5, 95% confidence interval (95%CI) 1.0-2.1). The area under the receiver-operating characteristics curve (AUC) was 0.67 (95%CI, 0.59-0.75) for hs-cTnI versus 0.59 (95%CI 0.51-0.67, p=0.012) for hs-cTnT. In contrast, among patients undergoing non-vascular surgery both preoperative hs-cTnI and hs-cTnT were independent predictors of the primary endpoint (aOR 1.6, 95%CI 1.3-2.0, and aOR 3.0, 95%CI 2.0-4.6, respectively) and showed higher predictive accuracy (AUC 0.77, 95%CI, 0.71-0.83, and 0.79, 95%CI 0.73-0.85, p=0.437).

Conclusions: Preoperative hs-cTnI and hs-cTnT predict major cardiac events after non-vascular surgery, while only hs-cTnI maintained prognostic accuracy also in patients undergoing vascular surgery.

Keywords: troponin; preoperative care; cardiac complications; non-cardiac surgery

Introduction

More than 300 million surgeries are performed annually worldwide[2]. Despite advances in surgery and anaesthesia, 30-day mortality after non-cardiac surgery remains substantial[98,99]. Cardiac complications, including perioperative myocardial infarction (MI), are important contributors to 30-day mortality[12,100]. Because cardiac complications, particularly MI, maybe silent and ECGs at one point in time can miss important changes, accurate detection mandates active surveillance. Predicting cardiac complications after non-cardiac surgery is difficult and inaccurate, as both patient and surgery related factors seem to matter. A recent multicentre study suggested that multivariate risk scores currently recommended have poor prognostic accuracy, particularly in patients undergoing vascular surgery[101]. Thus, it remains challenging to quantify the risk-benefit ratio of planned operations or to test interventions that might be preventative or therapeutic.

The use of cardiac biomarkers could improve the prediction of cardiac complications after non-cardiac surgery. Pilot studies by several groups including ours have suggested that preoperative high-sensitivity cardiac troponin T (hs-cTnT) blood concentrations seem to improve risk prediction in non-cardiac surgery when added to the Revised Cardiac Risk Index (RCRI)[31,41]. The role of high-sensitivity cardiac troponin I (hs-cTnI) in predicting cardiac complications after non-cardiac surgery remains largely unknown. It is also unknown, whether one cardiac troponin signal is more accurate than the other, and/or whether the type of surgery may impact on the relative accuracy of hs-cTnT versus hs-cTnI.

The aim of our study was to compare the accuracy of preoperative hs-cTnI and hs-cTnT for the prediction of major cardiac complications after non-cardiac surgery.

Methods

Patients

Between May 2014 and March 2016, patients undergoing non-cardiac surgery (vascular and non-vascular surgery) were studied in two University hospitals, including consecutive adult patients scheduled for planned or urgent, open or endovascular arterial vascular surgery at the Clinics Hospital, University of Sao Paulo Medical School, Brazil, and consecutive patients undergoing major non-cardiac surgery (vascular and non-vascular) from April to December 2015, at the University Hospital Basel, Switzerland. Inclusion criteria were age above 65 years OR and history of coronary artery disease, peripheral artery disease, or cerebrovascular disease.

For this analysis, we excluded patients with acute MI, stroke, or pulmonary embolism in the week preceding the operation because these events substantially influence both the risk of cardiac complications and blood concentration of cTnI and cTnT. For the main analysis, patients with missing hs-cTnI or hs-cTnT preoperative values were excluded.

Local ethics committees approved the protocol (EKNZ 2015/301 in Basel and CAPPESQ 610608 in Sao Paulo) and written informed consent was provided.

Perioperative assessment

Before surgery, clinical evaluation and an electrocardiogram (ECG) were performed. Patients' cardiac risk was classified based on the Revised Cardiac Risk Index (RCRI)[35]. Additional cardiac tests, such as echocardiogram or myocardial perfusion imaging tests, were performed at the discretion of the attending physician. Definitions of previous coronary artery disease (CAD), chronic heart failure (CHF) and anaemia are reported in the supplementary material online[73,102].

As recommended by our Institution and international guidelines, we used active surveillance in the detection of major cardiac complications after non-cardiac surgery[17,103]. Hs-cTnT blood concentrations were measured preoperatively, on the first and second postoperative day, and whenever symptoms suggestive of MI occurred. Routine 12-lead ECG was performed daily until the third postoperative day in Sao Paulo, in case of a relevant absolute increase in hs-cTnT (absolute change of 14ng/L or more) in Basel, and in both cohorts whenever symptoms suggestive of MI or arrhythmias occurred. Patients were followed-up for 30 days after surgery.

Troponin measurements

Blood samples for the determination of hs-cTnI (ARCHITECT High Sensitive STAT Troponin I assay, Abbott Laboratories) and hs-cTnT (Elecsys, Roche diagnostics, Mannheim, Germany) were collected once before surgery (within 30 days) and on the first and second postoperative days.

The hs-cTnI assay has a limit of blank (LoB) between 0.7-1.3ng/L, limit of detection (LoD) between 1.1-1.9ng/L and a 99th percentile upper reference limit (URL) of 13ng/L according to recent studies[104–109]. As other population studies had proposed a 99th percentile of 26ng/L[109], this cut-off was used for a secondary analysis reported in the supplementary material online. Sex-specific cut-offs are also available in the supplementary material online.

The hs-cTnT assay has a LoB of 3ng/L, a LoD of 5ng/L and a 99th percentile URL of 14ng/L.

In the cohort of vascular surgery patients, sensitive cardiac Troponin I (s-cTnI, Siemens Ultra, Advia Centaur immunoassay system) was also obtained. The s-cTnI assay has a LoD of 6ng/L and a 99th percentile of 40ng/L.

Clinical endpoints

The primary endpoint was a composite of major cardiac complications including cardiac death, cardiac arrest, perioperative MI, clinically relevant arrhythmias, and acute heart failure (AHF) within 30 days. Two independent physicians adjudicated all MI cases according to the criteria defined in the Third Universal Definition of Myocardial Infarction for spontaneous MI[17]. Accordingly, MI was diagnosed in patients with acute cardiomyocyte necrosis exceeding the 99th percentile of the hs-cTn assay, used in clinical practice in both centres (hs-cTnT), accompanied by either ischemic symptoms, new ECG changes or imaging evidence of loss of viable myocardium. Arrhythmia (atrial fibrillation/flutter, supraventricular tachycardia, ventricular tachycardia) was considered clinically significant if requiring drug therapy or electrical cardioversion. The attending cardiologist diagnosed AHF using clinical symptoms, physical examination, chest x-ray, BNP or NT-proBNP blood concentrations, and echocardiography[102,110,111]. Deaths were considered cardiovascular in the absence of a clear non-cardiac cause, as suggested in recent recommendations[62]. The secondary endpoint was all-cause mortality within 30 days of surgery. Patients were followed-up in outpatient clinic consultations, by phone, or by contacting their primary care physician. Additionally, study personnel requested reports from the general practitioners, treating facilities or death registries.

Statistical analysis

Categorical variables are shown as numbers and percentages and were compared by Fisher's exact test. Continuous variables are presented as medians and interquartile range (IQR) and were compared by Mann-Whitney-U test.

Based on our recent finding of very high cardiac event rate in patients undergoing vascular surgery and very poor accuracy of existing risk prediction tools in these patients[101], we prospectively decided to stratify the analysis according to the type of surgery (vascular versus non-vascular). We calculated the interaction p-value for the prognostic value of hs-cTn with the type of surgery for the combined endpoint using a binary logistic regression model.

We did multivariable binary logistic regression analysis for each available troponin assay adjusted for a selection of predefined covariables (age, sex, CAD, CHF, stroke, diabetes mellitus, hypertension, dialysis, and anaemia). Covariables were chosen by best predictive value for the primary endpoint and according to the number of events (one covariable per 10 events).

Receiver operating characteristic curves (ROC) were constructed to assess accuracy of the troponin assays for prediction of primary endpoint, and compared by de Long method. Then, we combined each troponin assay with the RCRI (by calculating mean predicted values using binary logistic regression), and evaluated whether there was improvement of risk prediction. Troponin values were log-transformed for this analysis and for the models. We also performed correlation analysis of preoperative hs-cTnI, hs-cTnT, haemoglobin, and estimated glomerular filtration rate (eGFR, calculated by CKD-EPI formula) values by Spearman's test.

ROC analyses were repeated for the secondary endpoint all-cause death.

To further test the different behaviour of hs-cTnT in vascular and non-vascular patients, we performed a post-hoc analysis comparing AUC of hs-cTnT in vascular versus non-vascular patients, including all patients for whom preoperative hs-cTnT was available, irrespective of missing hs-cTnI values.

P-values of <0.05 were considered to indicate statistical significance. Analyses were performed using SPSS 22 (IBM Co, NY, USA) and R software (version 3.1.3, "pROC")[81].

Results

Baseline characteristics

Flowchart of patient's inclusion is shown in **Supplement Figure A**. Baseline characteristics of the 1022 patients included in the main analysis are shown in **Table A**. Detailed surgical characteristics are shown in **Supplement Table A**. In brief, 243 patients underwent vascular surgeries (mainly open or endovascular aortic aneurysm repair, lower extremity bypass, or carotid surgery) and 779 patients underwent non-vascular surgeries (mainly orthopaedic/trauma, urologic, spinal, or visceral surgery). 807 (79%) surgeries were planned, and the remaining 215 (21%) were urgent or emergent.

Preoperative levels of troponin

Preoperatively, hs-cTnI levels were detectable in 100%, hs-cTnT levels in 98%, and s-cTnI in 60% of patients. Absolute levels are shown in **Supplement Table B**. The prevalence of baseline cTn levels above the 99th percentile was lower for hs-cTnI than for hs-cTnT assay (**Figure A**).

Overall, correlation between hs-cTnI and hs-cTnT values was good (r>0.6) and comparable in vascular and non-vascular subgroups. Hs-cTn levels were also correlated with eGFR and haemoglobin (**Supplement Table C**).

Clinical outcomes

The primary combined endpoint of major cardiac complications occurred in 108/1022 (10.6%, 95%CI 8.8-12.7) patients, with events occurring four-times more often after vascular surgery with an incidence of 58/243 (24%, 95%CI 19.0-29.9) versus 50/779 (6.4%, 95%CI 4.9-8.4, p<0.001) after non-vascular surgery (**Table B**).

Prediction of the primary endpoint: major cardiac complications

Patients with major cardiac complications had higher baseline median cTn blood concentrations with all assays than patients without complications. In vascular surgery patients, median baseline hs-cTnI was 8ng/L (IQR 4-15) vs. 5ng/L (IQR 3-8; p<0.001), median hs-cTnT was 14ng/L (IQR 9-19) vs. 10ng/L (IQR 6-17; p=0.039) and median s-cTnI was 11ng/L (IQR 6-23) vs. 7ng/L (IQR 6-14; p=0.002), respectively for patients with vs without cardiac complications.

In non-vascular surgery patients, median baseline hs-cTnI was 12ng/L (IQR 7-29) vs. 4ng/L (IQR 2-8; p<0.001) and median hs-cTnT was 40ng/L (IQR 15-64) vs. 13ng/L (IQR 7-22; p<0.001), respectively.

In vascular surgery patients, the prognostic accuracy for major cardiac complications of hs-cTnI was higher than hs-cTnT, with an AUC of 0.67 (95%CI 0.59-0.75) versus 0.59 (95%CI 0.51-0.67, p=0.012, **Figure B**).

In non-vascular surgery patients, the overall AUC was higher than in vascular surgery and hs-cTnI and hs-cTnT showed comparable AUCs of 0.77 (95%CI 0.71-0.83) versus 0.79 (95%CI 0.73-0.85, p=0.437, **Figure B**).

We found a significant interaction p-value for hs-cTnI (p=0.011) as well as hs-cTnT (p<0.001) with the type of surgery in regard to predictive value for major cardiac complications.

In multivariable analysis, in vascular surgery patients, only baseline hs-cTnI (but not hs-cTnT) remained an independent predictor of the primary endpoint (**Table C**), while in non-vascular surgery patients, both baseline hs-cTnI and hs-cTnT were independent predictors of major cardiac complications (**Table D**).

In vascular patients, the RCRI showed a comparable predictive accuracy as quantified by AUC compared to hs-cTnI, hs-cTnT, and s-cTnI. Combination of RCRI and cTn yielded non-significantly improved AUCs (**Figure C**). In contrast, in non-vascular patients, the RCRI showed a significantly lower AUC than hs-cTnI (p=0.04) and hs-cTnT (p=0.01) and adding RCRI to hs-cTn measurements did not improve the AUC (**Figure C**).

In the ancillary analysis of all patients with hs-cTnT values available (n=2495, **Supplement Figure A**), we found an AUC for hs-cTnT of 0.55 (95%CI 0.48-0.62) in vascular surgery patients versus 0.75 (95%CI 0.70 – 0.79; p <0.001) in non-vascular surgery patients.

Prediction of the secondary endpoint: all-cause mortality

All-cause mortality occurred in 33/1022 (2.9%) of all patients within 30-days, significantly more often in patients undergoing vascular surgery (8% vs 2%, p<0.001). Preoperative hs-cTnI, hs-cTnT, and s-cTnI concentrations provided comparable accuracy in the prediction of all-cause mortality in vascular surgery patients, but in non-vascular surgery hs-cTnT showed a markedly higher AUC than hs-cTnI, despite being non-significant with p=0.05 (**Figure D**).

Postoperatively, considering peak values in the first 3 days after surgery, the number of patients with values above 99th percentile increased for all assays in both cohorts (**Figure A**). Using the peak postoperative troponin values, all assays could predict 30-day mortality with good accuracy in both cohorts (**Supplement Figure B**).

Discussion

To the best of our knowledge this is the first study directly comparing preoperative hs-cTnI and hs-cTnT measurements in the prediction of major cardiac complications after non-cardiac surgery. We report four major findings. First, although using a biological equivalent 99th percentile cut-off concentration for hs-cTnI and T consistently documented in two recent large studies[104,108], preoperative hs-cTnT elevations were more than twice as common as preoperative hs-cTnI elevations. This finding emerged irrespective of the type of surgery. Second, the absolute increase in hs-cTn blood concentration was higher in patients undergoing vascular surgery as compared to non-vascular surgery, and this finding emerged for both hs-cTnI and hs-cTnT. Third, among patients undergoing vascular surgery, preoperative hs-cTnI, but not hs-cTnT, was an independent predictor of major cardiac complications. Fourth, among patients undergoing non-vascular surgery, both preoperative hs-cTnI and hs-cTnT blood concentrations were independent predictors of major cardiac complications after non-cardiac surgery.

This study corroborates and extends previous studies evaluating preoperative hs-cTnT measurements, and is the first to comprehensively evaluate hs-cTnI. Several previous studies addressed the role of hs-cTnT in non-cardiac surgery[31,41]. We have confirmed the findings of previous authors that 21-41% of patients have hs-cTnT levels above 99th percentile before surgery[30,40,65], and that this number can increase up to 45-60% after surgery. We have shown for the first time that high preoperative levels of hs-cTnI are less frequent than those of hs-cTnT. This finding is in line with a recent study evaluating prevalence of hs-cTn elevations in patients admitted to the hospital without acute coronary syndromes (ACS), in which the authors reported that elevations of hs-cTnT above the 99th percentile were present in more than one third of non-ACS patients whereas hs-cTnI elevations were present in only one tenth[112]. In another study evaluating only hs-cTnT in patients admitted to the emergency department due to non-ACS reasons, the authors found that half of the patients had hs-cTnT blood concentrations above 99th percentile[113].

In patients submitted to non-cardiac surgery, it has been shown that preoperative hs-cTnT is a predictor of post-operative cardiac complications[31,41], and our study corroborates with this finding. In the subgroup of patients undergoing vascular surgery, although it seems clear that an elevated hs-cTnT value before or after surgery is a predictor for short- and long-term all-cause mortality, there is still conflicting evidence regarding the role of preoperative hs-cTnT elevations in predicting cardiac complications, including perioperative MI[40,46,65]. We have demonstrated that preoperative hs-cTnT values have different predictive value in patients undergoing vascular and non-vascular surgery. In vascular patients, although preoperative

hs-cTnT is not a good predictor of major cardiac complications, it is good for predicting all-cause mortality. In contrast, in non-vascular surgery patients, both preoperative hs-cTnI and T are also good predictors for cardiac complications. We have confirmed these findings in an additional analysis of all patients for whom only hs-cTnT was available. One possible explanation is that the mechanism of perioperative MI may be different in vascular and non-vascular surgery patients. Vascular patients have more severe diffuse atherosclerotic disease and the procedure itself, including manipulation of the arterial bed, could trigger processes leading to plaque rupture and type 1 MI[13]. Therefore, preoperative baseline hs-cTnT values (maybe a surrogate for patients with more severe systemic disease) are less useful predictors for cardiac complications after vascular surgery, and only hs-cTnI reached statistical significance in our cohort. On the other hand, patients submitted to non-vascular surgeries were older and had less previous coronary events but more severe systemic disease, which could lead to a type 2 MI, AHF, or arrhythmias[65,114]. Therefore, in non-cardiac surgery patients, blood concentration of hs-cTnT can predict cardiac events as well as hs-cTnI.

These findings highlight the differences between the information provided by hs-cTnI and hs-cTnT in the perioperative setting. We explored the correlation between hs-cTnI and hs-cTnT in both cohorts and found it to be weaker than in studies enrolling patients presenting with suspected MI to the emergency department[104,115]. Hs-cTnT seemed more strongly correlated to renal dysfunction and anaemia than hs-cTnI, confirming initial pilot findings in patients hospitalized without acute coronary syndromes[112]. This may indicate that cTnT levels suffer more interference from non-cardiac factors than cTnI, and high levels of hs-cTnT may be related to severe systemic, non-coronary conditions. This could in part also explain the observation of a numerically higher prognostic performance for all-cause death observed in our study.

There are some possible explanations for potential differences in the information provided by cTnI and cTnT. First, cTnT exists in both cardiac and skeletal muscles of the foetus[116]. In patients with inflammatory muscular diseases, silent genes that codify cTnT in skeletal muscles can be reactivated leading to elevated hs-cTnT values[42]. Further findings of markedly elevated hs-cTnT levels in patients with peripheral artery disease and limb ischemia raise the hypothesis that this might influence the predictive accuracy in vascular patients[117]. However, this has to be investigated in more detail before conclusions can be drawn. Cardiac troponin I seems to be exclusively released by myocardial cells, so its release may be more specific for heart diseases[42]. Second, the mechanism responsible for release of cTn of the heart may be due to direct cardiomyocyte injury caused by systemic conditions, such as sepsis or inflammation[55], independent of the presence of CAD. Previous

biochemical studies have showed that correlation between different hs-cTnI assays is better than between hs-cTnI and T, and that these differences cannot be explained by analytical imprecision alone, therefore, implying a biological difference in the release mechanism of cTnI and T[118].

Additionally, we have confirmed that preoperative and peak postoperative hs-cTnT levels have good accuracy for prediction of 30-day all-cause mortality[30,31,40,41,46,65]. Postoperative blood concentrations of hs-cTnI and hs-cTnT were even more accurate predictors of 30-day mortality as these also potentially reflect the extent of cardiomyocyte injury caused by intraoperative complications including bleeding, hypotension, and cardiac arrhythmias. Patients submitted to vascular surgery had a higher increase in cTn blood concentrations in both assays, probably due to these intraoperative variables.

Overall, measurement of hs-cTn preoperatively improves the prediction of cardiac complications after non-vascular surgery, and should be implemented in clinical practice, since it is better than currently used risk scores, such as the RCRI. In patients undergoing vascular surgery, hs-cTnI may be preferable than hs-cTnT. These biomarkers may be used not only to assess more accurately the risk-benefit of surgery, but also to recommend measures to reduce risk, such as giving statins, referring the patient to the intensive care unit after surgery and performing surveillance for improving diagnosis and treatment of cardiac events.

Several limitations should be considered when interpreting our findings. First, the sample size of patients undergoing vascular surgery was only moderate. However, this seemed to have been compensated by the high event rate in these patients. Second, in the non-vascular surgery cohort, only high-risk patients defined as age ≥65 years or pre-existing atherosclerotic disease including CAD, cerebrovascular disease, or PAD were included. We can therefore not comment on the risk prediction in low-risk patients undergoing non-vascular surgery. Third, we measured both clinically available hs-cTn assays, one measuring hs-cTnI and one measuring hs-cTnT. Further studies are necessary to examine additional hs-cTnI and hs-cTnT assays that are in development. Fourth, it is possible that vascular patients were more closely monitored in routine clinical care as they are seen as high-risk cohort[25]. Therefore, the difference in event rate between vascular and non-vascular surgery may have been slightly overestimated.

Conclusion

In conclusion, preoperative hs-cTnI and hs-cTnT predict major cardiac events after non-vascular surgery, while only hs-cTnI maintained prognostic accuracy in patients undergoing vascular surgery.

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Conflicts of interest

Dr. Gualandro reports grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, a government research grant), Brazil , during the conduct of the study and personal fees from Servier, EMS, Sanofi, and Roche, outside the submitted work; Dr. Puelacher reports grants from PhD Educational Platform for Health Sciences (PPHS), outside the submitted work; Dr. Jaffe reports consulting from Beckman-Coulter, Roche, Alere, Siemens, Abbott, Shingotec Becton Dickinson, Singulex, NeurogenomeX, Outpost Medical, Novartis, during the conduct of the study; Dr. Twerenbold reports grants from Swiss National Science Foundation (Grant No P300PB-167803), personal fees from Roche Diagnostics, Abbott Diagnostics, Siemens, Brahms, outside the submitted work; .Dr. Calderaro reports grants from FAPESP, during the conduct of the study and personal fees from Bayer, outside the submitted work; Dr. Duarte reports grants from FAPESP, during the conduct of the study; Dr. Caramelli reports grants from FAEPSP and CNPq (National

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Tables

Table A Baseline characteristics, shown for the whole cohort and split according to surgery type. Data shown as counts (n) with percentage (%) or median with interquartile range (IQR)

	All Patients n = 1022	Vascular n = 243	Non-vascular n = 779	p-value
Male gender, n (%)	640 (63)	178 (73)	462 (59)	<0.001
Age (years), median (IQR)	72 [68-78]	68 [62-74]	74 [69-79]	<0.001
Diabetes mellitus, n (%)	282 (28)	89 (37)	193 (25)	<0.001
Hypertension, n (%)	718 (70)	204 (84)	514 (66)	<0.001
Coronary artery disease, n (%)	310 (30)	95 (39)	215 (28)	0.001
CABG/PCI, n (%)	183 (18)	52 (21)	131 (17)	0.104
Peripheral artery disease, n (%)	349 (34)	243 (100)	106 (13)	<0.001
Chronic heart failure, n (%)	148 (14)	39 (16)	109 (14)	0.465
Stroke/transient ischemic attack, n (%)	136 (13)	60 (25)	76 (10)	<0.001
COPD, n (%)	126 (12)	11 (5)	115 (15)	<0.001
Renal failure in dialysis, n (%)	14 (1)	8 (3)	6 (1)	0.007
Anaemia*, n (%)	456 (45)	86 (36)	370 (48)	<0.001
Preoperative medications				
Acetylsalacylic acid, n (%)	438 (43)	208 (86)	230 (30)	<0.001
Statins n (%)	552 (54)	221 (91)	331 (42)	<0.001
Betablockers, n (%)	431 (42)	125 (51)	306 (39)	0.001
ACEI or ARB, n (%)	552 (54)	150 (62)	402 (52)	0.006
Revised cardiac risk index				
I	361 (35)	25 (10)	336 (43)	<0.001
II	352 (34)	86 (35)	266 (34)	
III	208 (20)	84 (35)	124 (16)	
IV	101 (10)	48 (20)	53 (7)	
Laboratory assessment				
Creatinine (mg/dL), median (IQR)	0.94 [0.76-1.23]	1.14 [0.92-1.36]	0.9 [0.72-1.14]	<0.001
eGFR (ml/min)	73 [54-88]	64 [49-80]	77 [56-88]	<0.001
Haemoglobin* (g/dL), median (IQR)	12.8 [11.2-14]	13.3 [12.1-14.2]	12.6 [10.9-13.9]	<0.001

*n=1020; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; eGFR = estimated glomerular filtration rate

Table B Clinical outcomes within 30 days, shown for full cohort and split for surgery type

	All patients n = 1022	Vascular surgery n = 243	Non-vascular n = 779	p-value
Major cardiac complication	108 (11%)	58 (24%)	50 (6%)	<0.001
Cardiovascular death	11 (1%)	4 (2%)	7 (1%)	0.302
Cardiac arrest	8 (1%)	3 (1%)	5 (1%)	0.404
Myocardial infarction	57 (6%)	32 (13%)	25 (3%)	<0.001
Acute heart failure	37 (4%)	23 (45%)	14 (2%)	<0.001
Arrhythmia	24 (3%)	18 (49%)	6 (1%)	<0.001
All-cause mortality	33 (3%)	19 (8%)	14 (2%)	<0.001

Comparison done with Fisher's exact test; multiple events possible in one patient

Table C Multivariable logistic regression models using different cardiac troponin assays for prediction of major cardiac complications in vascular patients; hs-cTn = high-sensitivity cardiac troponin; logn = natural logarithm; s-cTn = sensitive cardiac troponin

Models predicting combined endpoint vascular surgery	Odds ratio (95%CI)	p-value
Model with hs-cTnI		
Hs-cTnI, per logn increase	1.5 (1.0-2.1)	**0.035**
Age, per year	1.0 (1.0-1.1)	0.071
Sex - male	1.5 (0.7-3.0)	0.284
Coronary artery disease	1.5 (0.8-2.9)	0.222
Chronic heart failure	1.9 (0.9-4.3)	0.112
Renal failure in dialysis	2.3 (0.5-11.3)	0.301
Model with hs-cTnT		
Hs-cTnT, per logn increase	1.0 (0.6-1.7)	0.970
Age, per year	1.0 (1.0-1.1)	**0.024**
Sex – male	1.5 (0.7-3.0)	0.286
Coronary artery disease	1.6 (0.8-3.1)	0.156
Chronic heart failure	2.4 (1.1-5.3)	**0.031**
Renal failure in dialysis	3.4 (0.6-20.4)	0.173
Model with sensitive cTnI		
S-cTnT, per logn increase	1.4 (0.8-2.3)	0.188
Age, per year	1.0 (1.0-1.1)	**0.022**
Sex – male	1.4 (0.7-3.0)	0.340
Coronary artery disease	1.7 (0.8-3.3)	0.140
Chronic heart failure	1.9 (0.8-4.5)	0.137
Renal failure in dialysis	2.6 (0.5-12.8)	0.247

logn = natural logarithm; 95%CI = 95% confidence interval

Table D Multivariable logistic regression models using different cardiac troponin assays for prediction of major cardiac complications in non-vascular surgery patients; hs-cTn = high-sensitivity cardiac troponin; logn = natural logarithm

Models predicting combined endpoint non-vascular surgery	Odds ratio (95%CI)	p-value
Model with hs-cTnI		
Hs-cTnI, per logn increase	1.6 (1.3-2.0)	**<0.001**
Age, per year	1.0 (1.0-1.1)	0.094
Stroke/transient ischemic attack	2.3 (1.1-4.8)	**0.035**
Diabetes mellitus	3.3 (1.8-6.1)	**<0.001**
Anaemia	3.0 (1.4-6.4)	**0.004**
Model with hs-cTnT		
Hs-cTnT, per logn increase	3.0 (2.0-4.6)	**<0.001**
Age, per year	1.0 (1.0-1.1)	0.182
Stroke/transient ischemic attack	2.5 (1.2-5.5)	**0.019**
Diabetes mellitus	2.8 (1.5-5.2)	**0.002**
Anaemia	2.0 (0.9-4.4)	0.077

logn = natural logarithm; 95%CI = 95% confidence interval

Figures

Figure A Prevalence of cardiac troponin (cTn) levels above the 99th percentile before and after vascular and non-vascular surgery, shown for high-sensitivity cTn (hs-cTn) I and T as well as sensitive-cTnI in for vascular surgery patients

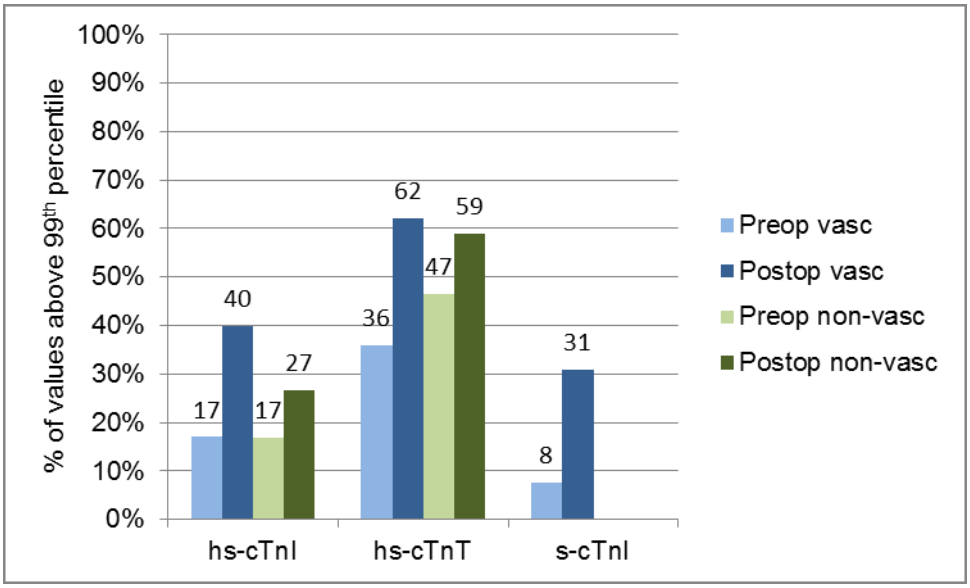


Figure B Area under the receiver operating characteristics curves (AUC) of the different troponin assays measured preoperatively for prediction of cardiac complications following A) vascular; and B) non-vascular surgery, shown with 95% confidence intervals

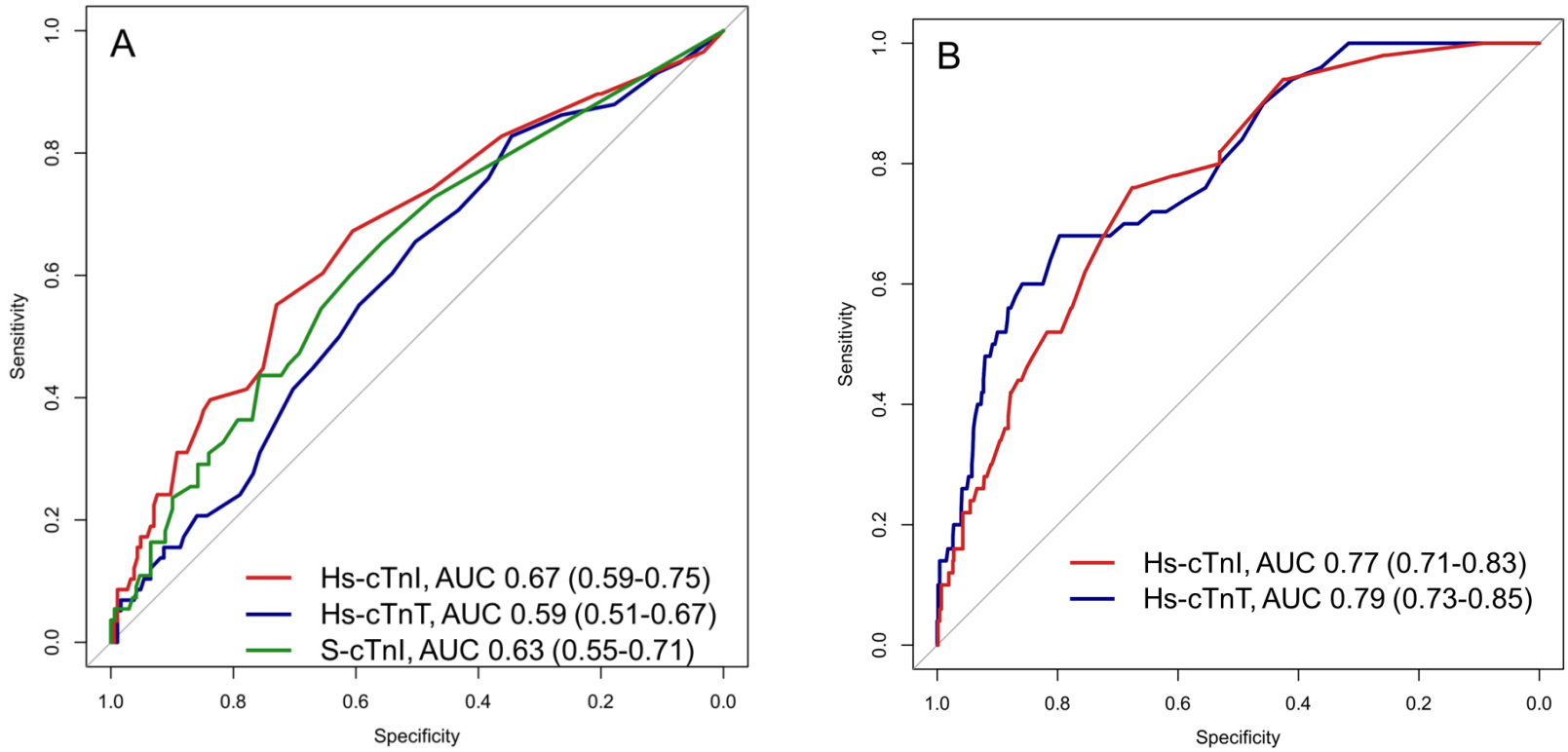
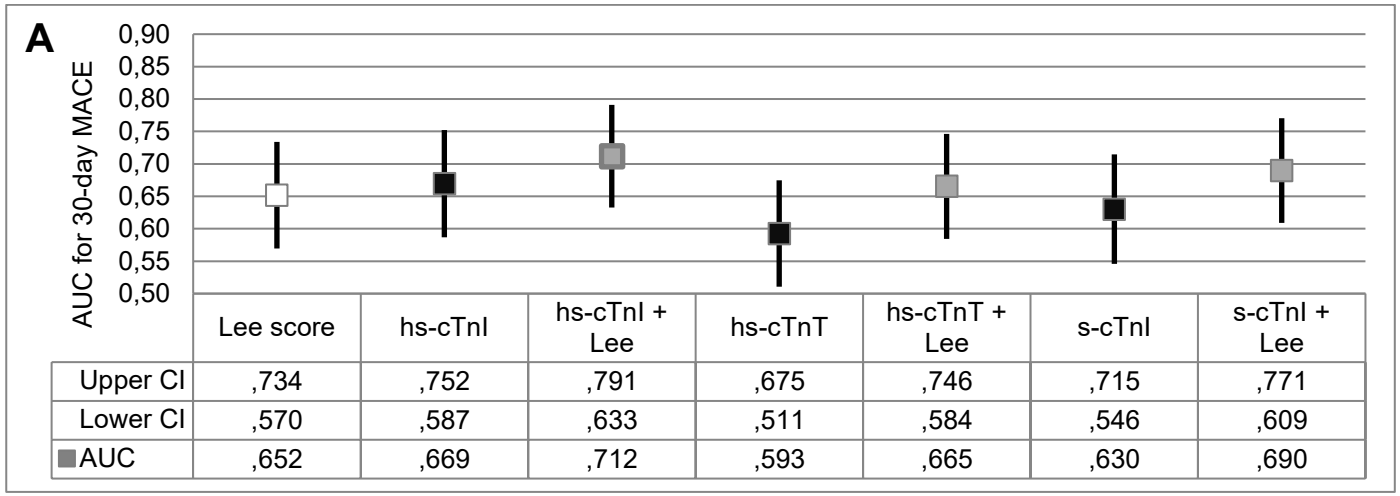
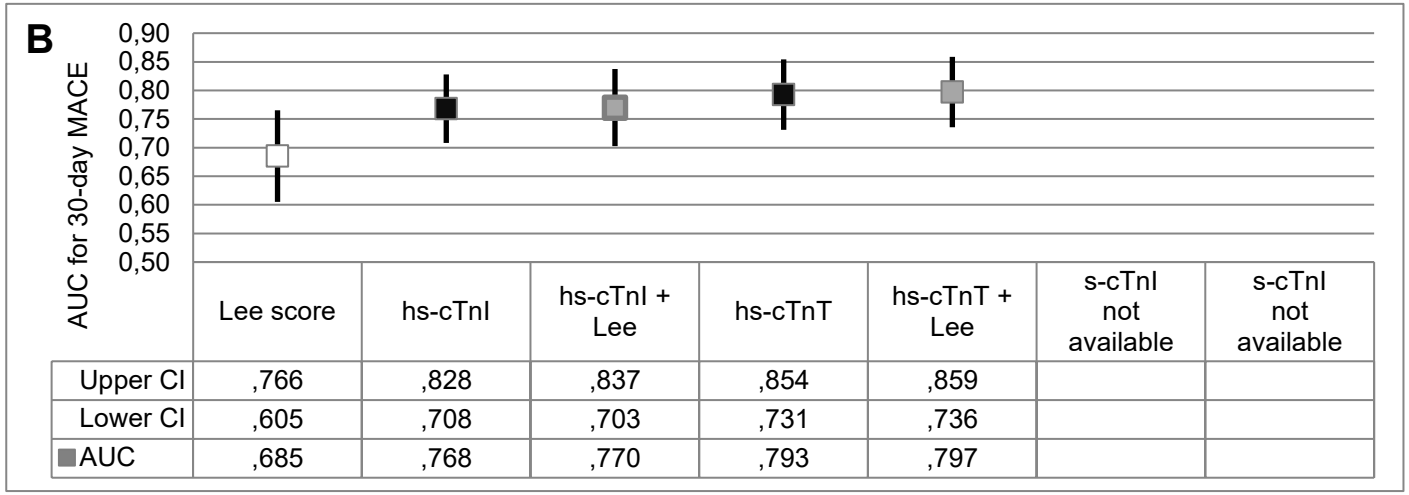


Figure C Area under the receiver operating characteristics curves (AUC) with 95% confidence intervals (CI) of cardiac troponin (cTn) assays, the Revised Cardiac Risk Index (Lee score), and the combinations of cTn and Lee score for prediction of primary endpoint for A) vascular; and B) non-vascular surgery patients

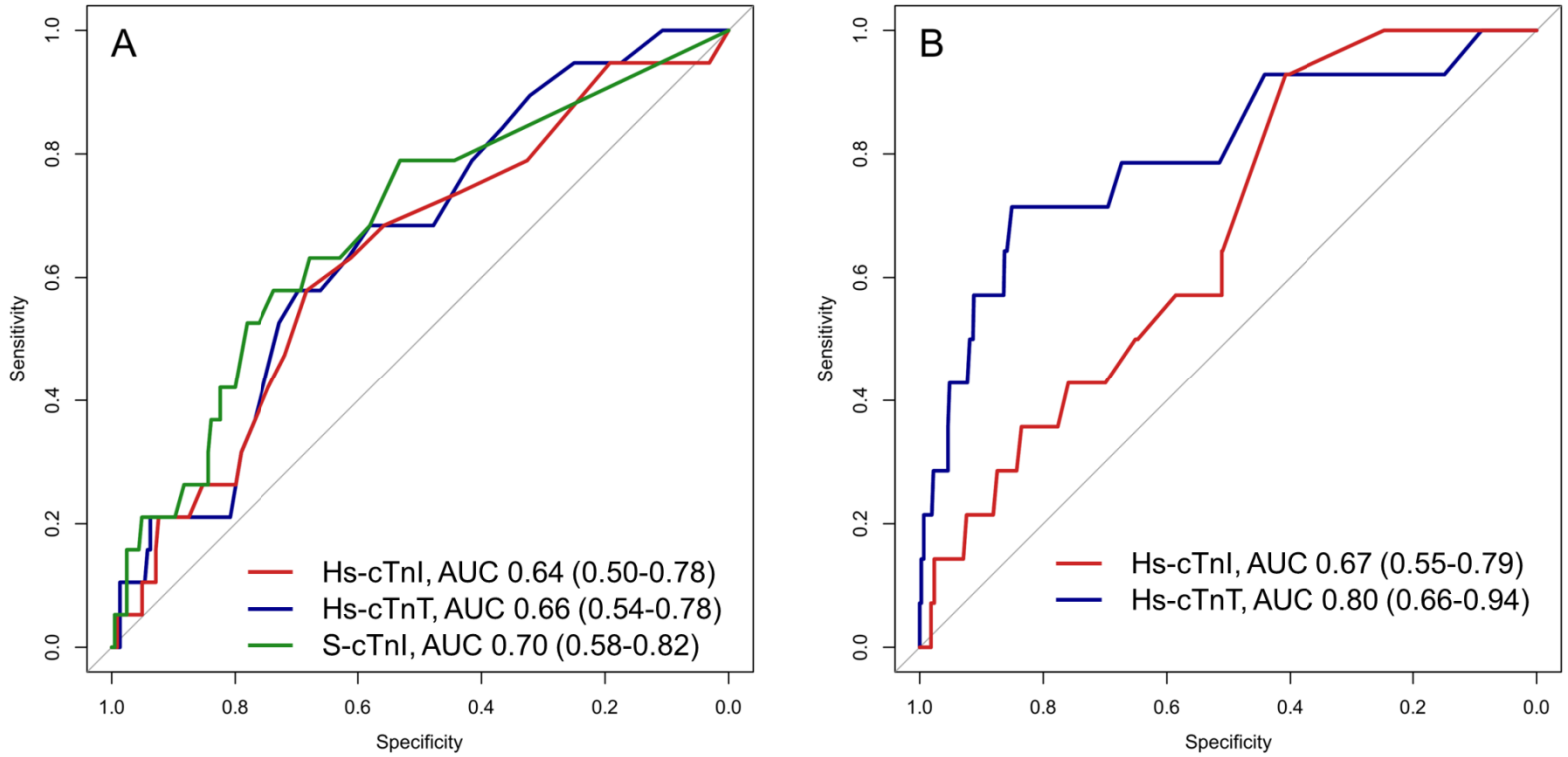


	Lee score	hs-cTnI	hs-cTnI + Lee	hs-cTnT	hs-cTnT + Lee	s-cTnI	s-cTnI + Lee
Upper CI	,734	,752	,791	,675	,746	,715	,771
Lower CI	,570	,587	,633	,511	,584	,546	,609
AUC	,652	,669	,712	,593	,665	,630	,690



	Lee score	hs-cTnI	hs-cTnI + Lee	hs-cTnT	hs-cTnT + Lee	s-cTnI not available	s-cTnI not available
Upper CI	,766	,828	,837	,854	,859		
Lower CI	,605	,708	,703	,731	,736		
AUC	,685	,768	,770	,793	,797		

Figure D Area under the receiver operating characteristics curves of the different troponin assays measured preoperatively for prediction of postoperative all-cause mortality in A) vascular; and B) non-vascular surgery patients, shown with 95% confidence intervals



Supplement

Perioperative assessment

Previous coronary artery disease (CAD) was considered in the presence of history of MI, chronic typical exercise-induced angina pectoris, previous coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention), or evidence of CAD in myocardial perfusion imaging (presence of fixed or reversible perfusion defects) or in coronary angiography.

Preoperative chronic heart failure (CHF) was considered if there were: clinical symptoms consistent with CHF, left ventricle ejection fraction (LVEF) lower than 50% assessed by echocardiography or LVEF lower than 45% assessed by GATED SPECT obtained during myocardial perfusion imaging. In cases with diagnostic uncertainty, B-type natriuretic peptide (BNP) or NT-proBNP were measured[102]. Anaemia was diagnosed according to WHO criteria as haemoglobin levels below 130g/L in men and 120g/L in women[73].

Troponin measurements

After blood collection, one aliquot of the blood sample was immediately processed, from which hs-cTnT was measured. In Basel, hs-cTnI was also measured from this sample; in Sao Paulo hs-cTnI was measured from serum that was frozen at -80°C in a batch. Prior the analysis, samples were homogenized by inversion and centrifuged at 3,000g for 10 minutes in order to remove particulate matter.

Supplement Table A Types of vascular and non-vascular procedures

Type of surgery	Frequency, n (%) n = 1022
Vascular surgeries	
Aortic aneurysm	95 (9)
Peripheral artery disease	74 (7)
Carotid stenosis	65 (6)
Other vascular	9 (1)
Non-vascular surgeries	
Orthopedic/Trauma	246 (24)
Spinal	142 (14)
Thoracic	84 (8)
Urologic	176 (17)
Visceral	106 (10)
Other non-vascular	25 (2)

Supplement Table B Blood concentration of cardiac troponin (cTn) measured by different assays and absolute number of patients above the 99th-percentile cut-off, shown for the whole cohort and according to surgery type

	All Patients n = 1022	Vascular n = 243	Non-vascular n = 779	p-value
Preoperative measurements				
High-sensitivity cTn I				
Preoperative level, ng/L	5 (3-9.4)	5 (3-10)	4 (3-9)	0.038
Above cut-off (>13ng/L), n (%)	171 (17)	40 (17)	131 (17)	1
Above cut-off (>26ng/L), n (%)	84 (8)	18 (7)	66 (8)	0.689
Above sex specific (>34/16ng/L), n (%)	119 (12)	23 (10)	96 (12)	0.253
High-sensitivity cTn T				
Preoperative level, ng/L	13 (7-22)	11 (7-18)	13 (8-24)	0.002
Above cut-off (>14ng/L), n (%)	450 (44)	87 (36)	363 (47)	0.003
Sensitive cTn I				
Preoperative level, ng/L	-	8 (6-16)*	-	-
Above cut-off (>40ng/L), n (%)	-	17 (8)*	-	-
Postoperative measurements				
High-sensitivity cTn I				
Postoperative peak level, ng/L	7 (4-17.5)	10 (5-26)	6 (4-15)	<0.001
Above cut-off (>13ng/L), n (%)	282 (30)	95 (40)	187 (27)	<0.001
Above cut-off (>26ng/L), n (%)	164 (17)	58 (24)	106 (15)	0.002
Above sex specific (>34/16ng/L), n (%)	213 (23)	75 (31)	138 (20)	<0.001
High-sensitivity cTn T				
Postoperative peak level, ng/L	18 (10-32)	19 (12-35)	17 (10-31)	0.043
Above cut-off (>14ng/L), n (%)	609 (60)	150 (62)	459 (59)	0.453
Sensitive cTn I				
Postoperative peak level, ng/L	-	21 (12-68)*	-	-
Above cut-off (>40ng/L), n (%)	-	68 (30)*	-	-

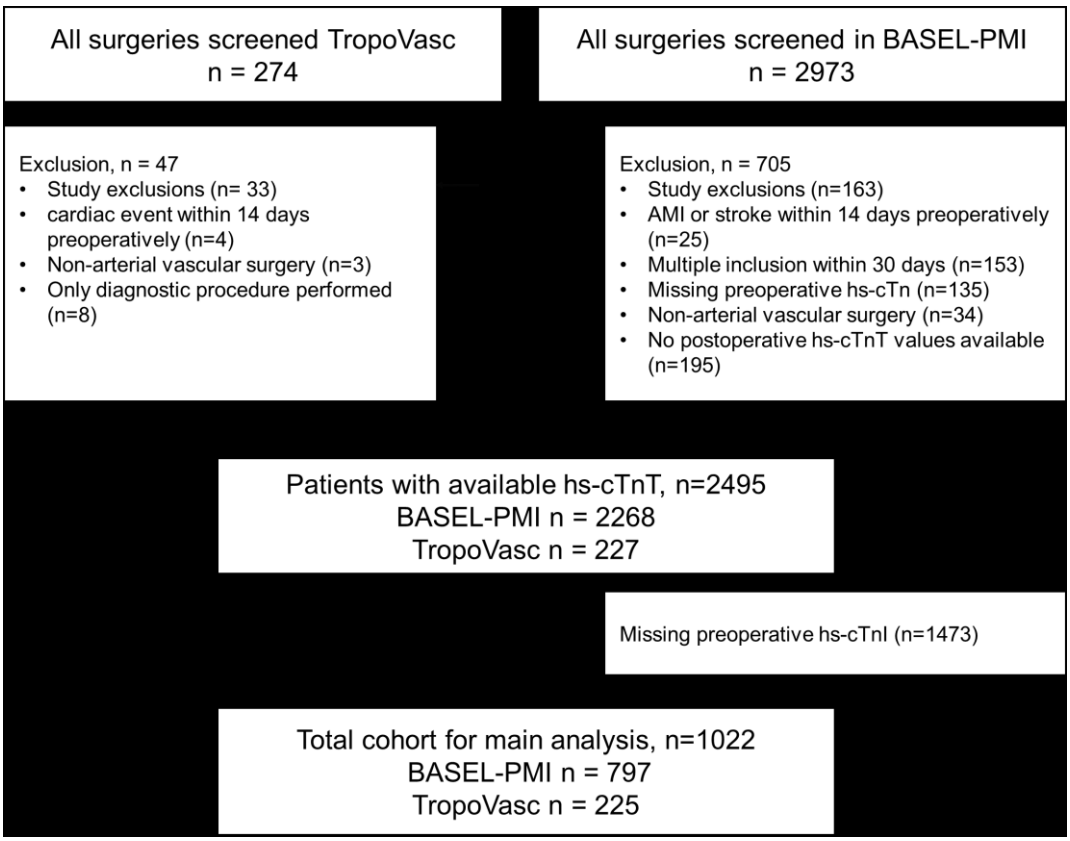
IQR=interquartile range; *n=224

Supplement Table C Correlation of cardiac troponins I and T with each other and other biochemical signals, split for vascular surgery and non-vascular surgery; all correlations p<0.001

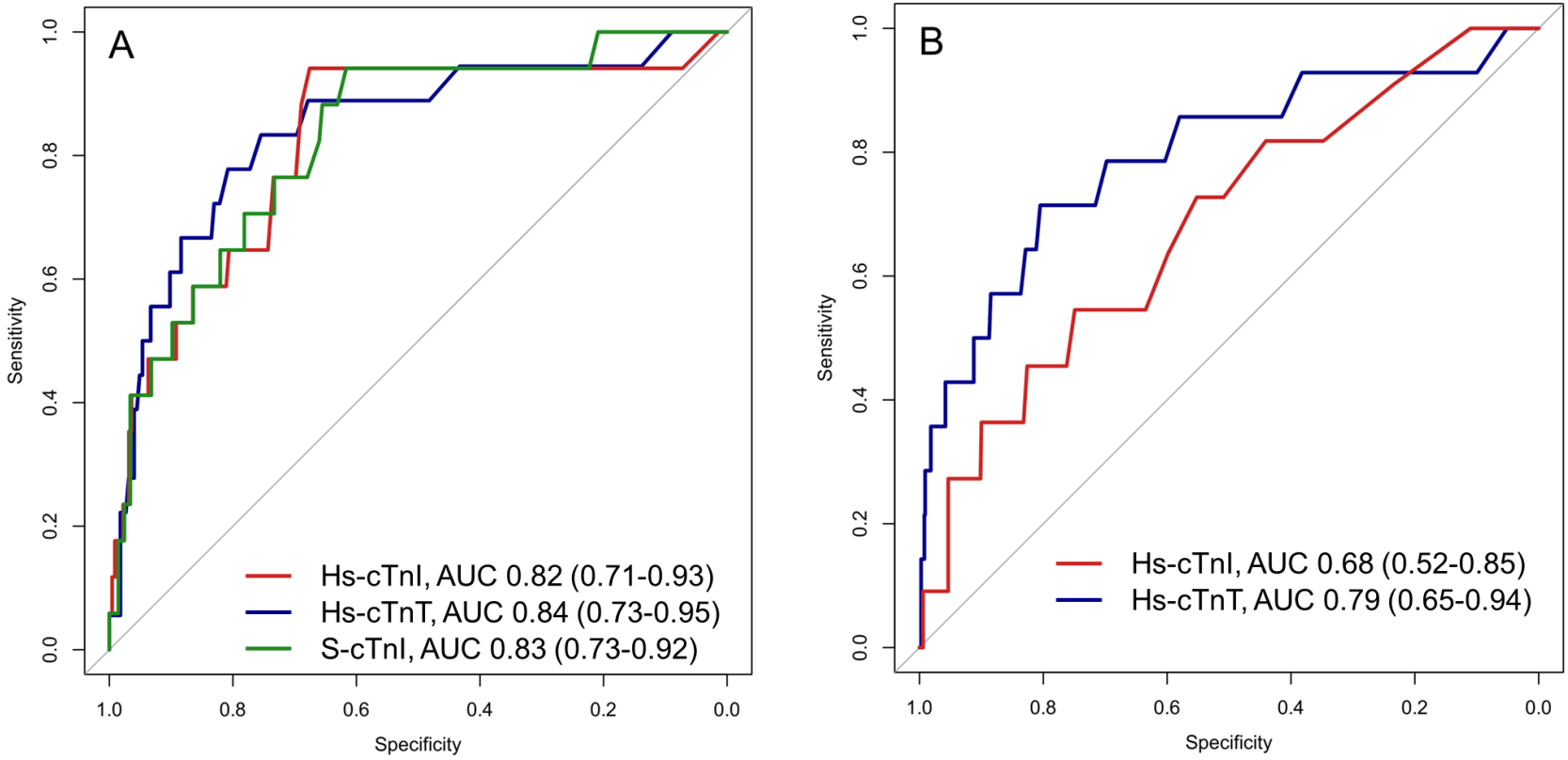
	hs-cTnI	hs-cTnT	eGFR	Hemoglobin
Vascular surgery				
hs-cTnI	x	0.64	-0.37	-0.16
hs-cTnT	0.64	x	-0.42	-0.26
Non-vascular surgery				
hs-cTnI	x	0.68	-0.32	-0.28
hs-cTnT	0.68	x	-0.39	-0.41

hs-cTnT = high sensitivity cardiac troponin T; hs-cTnI = high sensitivity cardiac troponin I; eGFR = estimated glomerular filtration rate, calculated with the CKD-EPI formula

Supplement Figure A Patient selection from the two studies; AMI = acute myocardial infarction, hs-cTn = high-sensitivity cardiac troponin



Supplement Figure B Area under the receiver operating characteristics curves (AUC) of peak postoperative measurements of the different troponin assays for prediction of postoperative all-cause death following A) vascular; and B) non-vascular surgery, shown with 95% confidence intervals



Discussion and Outlook

The aim of this PhD study was to contribute to improving perioperative care after non-cardiac surgery, by establishing a large prospective cohort study and investigating PMI. In the years since the conception of this study, an increasing number of publications have added to our understanding of this topic. Nonetheless, with our stringent methodology, large study size and international collaboration we were able to gain important and novel insights. To our knowledge, ours is to date the largest study using a prospective definition of PMI.

Novel insights into PMI

Incidence

We found that PMI is a common complication of non-cardiac surgery in high-risk patients, occurring in one out of seven patients. A wide range of PMI rates has been reported in recent literature[3,5,12,30,37], very possibly reflecting differences in patient population, surgical procedures and, most importantly, definitions of PMI. Different definitions have been proposed, but even in the largest cohort, the VISION study, which originally introduced a focus on maximum postoperative hs-cTn levels[3], more recent publications arising from the study have begun to incorporate change to preoperative levels as used in our study and others[12,65]. As this reflects injury time related to surgery instead of also chronic elevations, such a definition might be more appropriate than one using only postoperative values. For this reason, our data could substantially improve perioperative care by quantifying the incidence of PMI according to a clear cut-off level in line with the hs-cTn criterion used for the diagnosis of spontaneous AMI[17]. This could be easily replicated in future studies.

Outcome

We found that patients with PMI had a markedly increased 30-day mortality, a six-fold increase compared to patients without PMI. This estimate is probably lower than that of an unscreened population, as patients in our cohort were often seen by a cardiologist and had adaptations to their treatment regimen, something which is not routinely done in settings without systematic PMI detection. The excessive mortality associated with PMI persisted up to one year and was similar in asymptomatic PMI and PMI fulfilling any additional criteria required for spontaneous AMI[17], highlighting the relevance of PMI detected only by a hs-cTn criterion. These findings corroborate the finding of increased mortality associated with PMI, even though the range of estimates, as with incidence, varies according to studied population and definition of PMI. The consistency of an increased mortality associated with PMI

highlights the importance of PMI as a perioperative cardiac complication, and will hopefully spark future research from various research groups.

Subtypes

In order to shed light on the pathophysiology of PMI, we prospectively evaluated all cases and made a sub-characterisation of PMI cases according to suspected aetiology. The most common type of PMI (>80%) is the cardiac subtype, which is associated with an increased 30-day and continuously rising one-year risk compared to patients without PMI. This might reflect a mix of three factors: 1) increased acute mortality risk following the PMI, 2) increased long-term event rate resulting from a lack of treatment of myocardial injury, potentially leading to arrhythmias or heart failure, and 3) elevated overall risk reflecting the higher prevalence of comorbidities in patients experiencing a PMI. In contrast to this stand, PMI resulting from an extra-cardiac cause, e.g. severe sepsis, has a different outcome than those with a presumed cardiac cause, with a very high short-term mortality and a relatively stable mortality after the initial peak of up to one year after surgery. The initial mortality peak might reflect the very high mortality of the extra-cardiac disease, such as severe sepsis which usually has a mortality rate of between 4–42% despite intensive care, including close monitoring in an intensive care unit, optimal medical treatment, and follow-up[119,120]. However, after the event the causative agent of increased mortality can usually be regarded as resolved in survivors, therefore mortality after discharge is low. Hypothetically, translating this benefit to cardiac PMI identification and evidence based treatment of PMI might improve outcomes in cardiac PMI.

Making use of hs-cTn preoperatively

PMI appears to be reliably detected only with the use of systematic hs-cTn screening[4], therefore measuring hs-cTn in the perioperative setting should be considered in routine clinical practise. The successful implementation of such a screening was an important step in showing that screening that includes preoperative measurements can be successfully implemented. To date, the screening has been conducted in >7000 cases at the University Hospital in Basel and was also successfully implemented in an external center, the Kantonsspital Aarau, where >1500 cases have been screened since its implementation in 2016. We have published our internal standards to encourage more widespread use of PMI screening[121]. When implementing such a screening, it is important to make best use of the additional information provided by cTn, ideally preoperatively. Therefore we wished first to validate commonly used risk scores, especially the Lee score[35,72], and then to combine the scores with the information gained from hs-cTn. In our study, the evaluated scores offered a

moderate discrimination between patients according to their risk, but severely underestimated the absolute risk, especially in the groups labelled “low-risk”. As we could not validate the scores, owing particularly to a lack of calibration of the scores predicting rates of up to ten-fold lower than observed, there is clearly a need to recalibrate established scores or to derive new risk scores. One attractive option for improving the predictive accuracy would be to use the prognostic value of preoperative hs-cTn, which was demonstrated in earlier studies[31,41]. We found that hs-cTnT and I were both useful in predicting all-cause death and postoperative MACE. As the prognostic value offered by hs-cTns appeared to be comparable or even superior to that of conventional risk scores, we believe that hs-cTn could be a valuable component of future preoperative risk stratification. The question of whether to use hs-cTnT or hs-cTnI depends, we believe, on the population, with hs-cTnI providing additional value in vascular surgery patients, as well as on the endpoint that should be predicted, with hs-cTnT potentially offering benefits in the prediction of all-cause mortality. Better assessment of the risk-benefit ratio of a surgical procedure is expected to help patients and physicians to make an informed decision on performing elective surgery in patients at high risk of MACE following non-cardiac surgery. Given the growing concern about unnecessary surgical operations performed in high-income countries such as Switzerland and the United States[122], this could not only help to prevent major harm to patients, but might also reduce costs to the health care system; first by avoiding the cost of unnecessary surgery and secondly by avoiding costs related to MACE, including PMI following non-cardiac surgery. Better risk-stratification provided by new scores could help to base the medical and political decisions on which hospital should provide what medical service on a more insightful foundation. For instance, major non-cardiac surgery in patients at high risk of developing MACE following non-cardiac surgery should possibly be offered only at a small number of dedicated hospitals, while the same procedure in patients at much lower risk could well be justified in a regional hospital close to the patient’s home.

Future directions of research

The BASEL-PMI observational study is ongoing, having recruited over 8500 cases from two centres during the period of my PhD studies. The analyses presented in this thesis are the first major results from this study, with more analyses planned. Most important are the characterisation of PMI and the exploration of potential management strategies, as briefly discussed below.

Characterisation and pathophysiology of PMI

One central and pre-specified analysis of our study will be to further explore PMI and evaluate predisposing comorbidities as well as perioperative factors contributing to PMI. As screening cohorts of patients seems to be necessary for detection, knowing which groups are particularly susceptible to developing PMI is essential to inform the choice of target population for a screening, e.g. patients with coronary artery disease, chronic kidney disease or diabetes[7,46].

Our knowledge of perioperative factors contributing to the occurrence of PMI is also limited. Without a clear identification of potentially modifiable contributors, it is currently difficult to implement preventive measures. In addition, identifying perioperative factors could further our understanding of the pathophysiology of PMI, which is believed to be a mix of injuries caused by plaque rupture (type I mechanism) and injuries caused by a supply-demand mismatch (type II mechanism)[11,13,17]. Our data should allow us to gain further insights into the presumed pathophysiology of PMI and potentially allow us to define further subtypes of cardiac PMI in particular.

Management strategies for PMI

The data generated in this study will be used to generate hypotheses for medical strategies to improve outcome after non-cardiac surgery. One example is the analysis of the effect of statins in the perioperative period. Multiple cardiovascular guidelines currently encourage the use of statins for prevention of adverse cardiac events for a wide range of diseases in the non-surgical setting[84,123–125]. Despite this established evidence of benefit in acute and chronic cardiovascular disease, the optimal perioperative use of statins remains unclear, partly as a result of controversy regarding the scientific integrity of several randomized clinical trials of perioperative statins[126]. Current perioperative guidelines addressing patients at cardiovascular risk undergoing non-cardiac surgery limit their recommendations to the continuation of an established statin therapy, and the potential initiation of therapy in patients undergoing vascular surgery[25]. This is based largely on two meta-analyses that found inconclusive evidence of the benefit of statins for prophylaxis of perioperative events[127,128], except in patients undergoing vascular surgery. New data emerging from observational studies and a small randomized trial, however, have shown potentially beneficial effects of perioperative statins in reducing postoperative mortality and the incidence of PMI[129,130]. In addition, observational evidence indicates a potential benefit of statin therapy following the occurrence of a PMI[6]. Promising strategies are candidates for future investigator initiated clinical trials, which could be conducted within the established and still expanding study network of BASEL-PMI.

Contributions by the PhD student

I was given the wonderful opportunity of being part of this study from its very onset and was able to contribute from the planning phase to the design and implementation, and finally to the analysis and writing up of this large observational study. In this nurturing environment, I was challenged and encouraged and played a substantial role in the development of the project plan, the study protocol and the ethics proposal and in the coordination of our study group, the implementation of the screening in the hospital and in the management of the growing BASEL-PMI on-site team.

I performed a thorough literature review (from which a narrative review was created[100]), drafted the first version of the study protocol, including endpoint definitions, pre-specified analysis plans for our main and secondary objectives and sample size estimation and I coordinated our study group during the drafting process. I drafted and submitted the ethics proposal and funding proposals to the Swiss National Science Foundation, the Swiss Heart Foundation, the proPatient foundation, the PhD Education Platform for Health Sciences and the University Hospital Basel. During the course of the study, I drafted and submitted three ethics amendments to our study protocol; these were to allow an extension of the study beyond the initial 3000 patients, to include an external centre, and to apply for a sub-study concerning reuse of routine sample material.

As study coordinator, I further developed the study infrastructure by selecting the study variables, creating and maintaining our study database and establishing contacts and interfaces with our clinical IT structure. I managed the data, conducted risk analyses and change management and wrote and curated the standard operating procedures. I also had a large part in the education of new study team members and conducted regular updates for the clinical teams, acting as a link between the clinical routine screening and our study team.

As part of our research team, I was involved in supervision of MD candidates and Masters students, with an emphasis on imparting research methodology and statistics skills, but also co-supervising Masters and MD-theses towards the end of my studies. Furthermore, I was part of the methodological and statistical support for other studies, helping to draft grant proposals (APACE, BASEL-VIII, BASEL-IX), writing ethics proposals, as well as providing methodological input, conducting specific analyses, double checking statistical analyses (as is customary in our group) and providing critical and constructive feedback on manuscript drafts. In order to further our collaboration with external partners, I performed a database merge with a study team from Sao Paulo and conducted analyses on the shared data file.

I learned many important aspects concerning the analysis of data and the drafting of manuscripts during my time as PhD candidate, both directly from my supervisor and from the close collaboration with him and other excellent researchers from my group and from international experts. I drafted pre-specified analysis plans and did highly exploratory work, drafted, submitted and revised manuscripts as first and co-first author and presented our work at international, national and local conferences in the form of talks and posters.

Conclusion and closing remarks

This PhD was the initial step in a concerted effort to improve perioperative care by generating essential knowledge on perioperative myocardial injury. In our observational study, which included nearly 3000 cases, we realised that PMI is very common after non-cardiac surgery and is associated with high short-term and long-term mortality. This excessive mortality rate is independent of whether patients with PMI fulfil any of the additional criteria required for spontaneous acute myocardial infarction, such as ischemic symptoms. As the majority of patients do not exhibit any ischemic symptoms, systematic screening should be considered for accurate detection of PMI. As a result of this under-detection, the incidence of PMI and therefore cardiac complications after non-cardiac surgery is currently underestimated and is not adequately represented in currently established risk scores. Increased awareness and consensus on a definition of PMI could to be important first steps towards improving perioperative care. This study provides important insights that will assist in achieving this goal. Future research concerning the detailed characterization of PMI and potential strategies to improve outcomes is necessary and are the planned next steps.

"If I have seen further, it is by standing on the shoulders of giants." – Sir Isaac Newton

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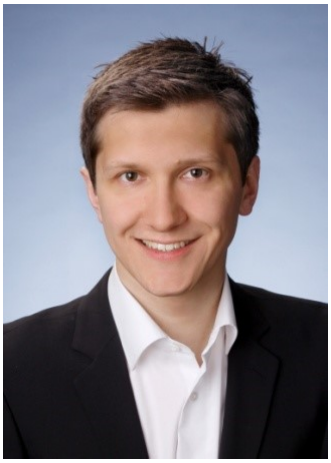
Curriculum vitae



Personal information

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Education

2014-2017	Doctoral studies for PhD, University Hospital Basel, Supervisor: Prof. Christian Müller, Switzerland
2013-2014	MD studies, University Hospital Basel, Supervisor: Prof. Christian Müller, Switzerland
2007-2013	Medical studies, Medical University Innsbruck, Austria
2006-2007	Community service Jugendrotkreuz Tirol, Austria
1998-2006	Akademisches Gymnasium Innsbruck, Austria

Employment history

2014-now	PhD candidate at the Cardiovascular Research Institute Basel, University Hospital Basel, Prof. Christian Müller
2013-2014	Science fellow at the Cardiovascular Research Institute Basel, University Hospital Basel, Prof. Christian Müller
2013-2013	Study coordinator for the ISCHEMIA trial, Medical University Innsbruck
2010-2013	Speaker at the “Institut für Studentenkurse”, Innsbruck, group and private tutoring
2006-2007	Community service Jugendrotkreuz Tirol

Language skills

German	Native
English	Fluent, CAE, eight years of bilingual education
French	Basic

Approved research projects

Basel Incidence, Patient Characteristics, Pathophysiology, and Outcome of Perioperative Myocardial Injury in Non-cardiac Surgery (BASEL-PMI, NCT02573532); prospective pragmatic observational study

Reliability of cardiac troponins for the diagnosis of myocardial infarction in the presence of rhabdomyolysis; retrospective cohort study

Supervision of junior researchers

Master students	Luca Osswald, Christina Hollenstein, Lukas Bock, Ekrem Temizel, Noemi Glarner, Saranya Thambipillai

Teaching activities

Academia	Methods- and statistics classes at Cardiovascular Research Institute, Basel Tutor at the Institute of Anatomy, Innsbruck
Industry	Speaker at the “Institut für Studentenkurse”, Innsbruck

Membership in panels, boards and scientific reviewing activities

Panel work	Student representative at PhD Educational Platform for Health Sciences, Basel
Peer-reviewer	American Journal of Cardiology, European Journal of Clinical Investigations

Active membership in scientific societies

None

Organisation of conferences

Courses	Handling of Missing Data, June 2017, PhD Methods-Journalclub Health Sciences 2015-2017

Prizes, awards, fellowships

Grants	PPHS Top-Up 2016 (9500 CHF)
Prizes	Best presentation, Clinical Research Day 2017 (2000 CHF)
Fellowships	VWFAWF PhD-Stipend 2016 (45000 CHF)

Career breaks

None

Clinical experience

2013-2017	Clinical researcher
2012-2013	Intern at internal medicine, general surgery, dermatology, psychiatry, primary care
2009-2011	Clinical traineeships: internal medicine, general surgery, gynaecology