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Identification of myocardial injury using perioperative troponin surveillance in major noncardiac surgery and net benefit over the Revised Cardiac Risk Index

Michelle S. Chew[1,*], Christian Puelacher[2], Akshaykumar Patel[3], Fredrik Hammarskjöld[4], Sara Lyckner[5], Malin Kollind[6], Monir Jawad[6,7], Ulrika Andersson[8], Mats Fredrikson[9], Jesper Sperber[5], Patrik Johnsson[10], Louise Elander[11], Jakob Zeuchner[11], Michael Linhardt[1], Lina De Geer[1], Wictor Gääw Rolander[1], Gunilla Gagnö[1], Helén Didriksson[1], Rupert Pearse[3], Christian Mueller[2] and Henrik Andersson[1]

[1]Departments of Anaesthesia and Intensive Care, Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden, [2]Cardiovascular Research Institute Basel and Department of Cardiology, University Hospital Basel, University Basel, Basel, Switzerland, [3]William Harvey Research Institute, Queen Mary University of London, London, UK, [4]Department of Anesthesiology and Intensive Care, Ryhov County Hospital, Jönköping, Sweden, [5]Department of Anesthesiology, Mälarsjukhuset, Centre for Clinical Research Sörmland, Eskilstuna, Sweden, [6]Department of Anaesthesia and Intensive Care, Centralsjukhuset Kristianstad, Kristianstad, Sweden, [7]Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden, [8]Department of Clinical Sciences Lund, Anaesthesiology and Intensive Care, Skåne University Hospital Lund, Lund University, Sweden, [9]Department of Clinical and Experimental Medicine, Faculty of Medicine and Health, Linköping University, Linköping, Sweden, [10]Department of Clinical Sciences, Anaesthesiology and Intensive Care, Skåne University Hospital Malmö, Lund University, Sweden and [11]Department of Anaesthesia and Intensive Care, Biomedical and Clinical Sciences, Vrinnevi Hospital, Norrköping, Sweden

*Corresponding author. E-mail: Michelle.chew@liu.se

Abstract

Background: Patients with perioperative myocardial injury are at risk of death and major adverse cardiovascular and cerebrovascular events (MACCE). The primary aim of this study was to determine optimal thresholds of preoperative and perioperative changes in high-sensitivity cardiac troponin T (hs-cTnT) to predict MACCE and mortality.
Methods: Prospective, observational, cohort study in patients $\geq$50 yr of age undergoing elective major noncardiac surgery at seven hospitals in Sweden. The exposures were hs-cTnT measured before and days 0–3 after surgery. Two previously published thresholds for myocardial injury and two thresholds identified using receiver operating characteristic analyses were evaluated using multivariable logistic regression models and externally validated. The weighted comparison net benefit method was applied to determine the additional value of hs-cTnT thresholds when compared with the Revised Cardiac Risk Index (RCRI). The primary outcome was a composite of 30-day all-cause mortality and MACCE.
Results: We included 1291 patients between April 2017 and December 2020. The primary outcome occurred in 124 patients (9.6%). Perioperative increase in hs-cTnT $\geq$14 ng L^{-1} above preoperative values provided statistically optimal model performance and was associated with the highest risk for the primary outcome (adjusted odds ratio 2.9, 95% confidence interval 1.8–4.7). Validation in an independent, external cohort confirmed these findings. A net benefit over RCRI was demonstrated across a range of clinical thresholds.
Conclusions: Perioperative increases in hsTnT $\geq$14 ng L^{-1} above baseline values identifies acute perioperative myocardial injury and provides a net prognostic benefit when added to RCRI for the identification of patients at high risk of death and MACCE.

Editor's key points

- Cut-off values for high-sensitivity cardiac troponin T (hs-cTnT) to define myocardial injury, especially as it relates to its prognostic value in identifying those at risk of major cardiac events or death, is unclear.
- The revised cardiac risk index is an established prognostic indicator of major cardiac events after surgery, but it has only moderate predictive utility.
- This study found that a perioperative elevation of hs-cTnT of $\geq$14 ng L^{-1} added clinically useful predictive value to the Revised Cardiac Risk Index.

Cardiac troponins (cTns), as quantitative markers of cardiomyocyte injury, are commonly elevated after noncardiac surgery.[1–6] The vast majority of patients do not fulfil the universal definition of myocardial infarction or experience ischaemic symptoms.[1–3,7] Yet, increased perioperative levels of cTns independently increase the risk of 30-day and long-term mortalities, and postoperative elevations are important indicators of poor outcome in otherwise asymptomatic patients.[1–8] Current guidelines recommend screening patients at high risk of cardiovascular complications by measurement of cTns.[9–11] However, screening is hampered by the lack of guidance regarding appropriate cut-off levels, the timing of measurements, and available interventions.

Limited data exist for the value of cTns when added on to the Revised Cardiac Risk Index (RCRI) for preoperative risk stratification. The independent prognostic value of increased cTns in the presence of other determinants of perioperative outcomes are also poorly understood.[12–14] Although there is a general consensus favouring the high-sensitivity troponin assays, various definitions and cut-off values have been applied in previous studies. Elevations in preoperative cTns also occur commonly[1–5,8,12] and may portend significant morbidity and mortality postoperatively.[3,8,12–17] This raises concerns for preoperative risk stratification and a potential dilemma for the management of these patients before surgery. Measurement of preoperative and postoperative cTns is advocated for perioperative screening to differentiate acute perioperative myocardial injury from pre-existing chronic myocardial injury. The association of acute perioperative myocardial injury with mortality, major adverse cardiovascular and cerebrovascular events (MACCE), or both has been demonstrated in several studies.[1–4,6,8,13] Puelacher and colleagues[3] found that the combination of increased preoperative high-sensitivity cardiac troponin T (hs-cTnT) and a perioperative change of $\geq$14 ng L^{-1} were associated with the highest risks for short- and long-term mortalities.[3] Other studies emphasise the role of postoperative cTn surveillance.[1,2,6] Notably, all studies have applied different criteria to define

perioperative myocardial injury and none have derived or externally validated diagnostic thresholds for the prediction of MACCE and mortality.

Thus, ambiguity still exists regarding timing and optimal threshold values of cTns for prediction of adverse cardiovascular outcomes. There are no comparative studies of perioperative cTn thresholds for the diagnosis of myocardial injury, and none of the established thresholds have been externally validated.

The primary aim of this study was to determine optimal thresholds of preoperative hs-cTnT and perioperative changes in hs-cTnT for the prediction of MACCE and mortality within 30 days after surgery. A secondary aim was to provide an external validation for the identified thresholds. Finally, we aimed to provide a decision analysis that may help clinicians compare the net benefit of using hs-cTnT when added to the RCRI.

Methods

We adhered to the STROBE and STARD reporting guidelines (Supplementary Table S1). The study was approved by the Regional Ethical Review Committee (Linköping, Sweden; March 29, 2017) and registered at clinicaltrials.gov (NCT03436238). All participants gave written informed consent.

We conducted a multicentre, prospective cohort study of patients aged $\geq$50 yr undergoing elective, major abdominal surgery and requiring at least one overnight hospital stay. Consecutive patients from seven hospitals in Sweden (three university and four regional hospitals) were included between April 2017 and December 2020. Major abdominal surgery was defined as major or complex major, according to the Surgical Outcome Risk Tool.[18] Baseline characteristics, and intraoperative and postoperative variables were recorded and RCRI calculated for all patients (Table 1). Preoperative anaemia was defined as haemoglobin <130 g L^{-1} for men and <120 g L^{-1} for women, preoperative increased creatinine was defined as plasma levels of creatinine $\geq$100 μmol L^{-1} for men and $\geq$90 μmol L^{-1} for women, intraoperative transfusion was defined as intraoperative transfusion of any blood product, and intraoperative hypotension was defined as MAP<55 mm Hg at any time intraoperatively (regardless of duration). The presence of ischaemic symptoms and 12-lead ECG were recorded up to 24 h before surgery, after surgery at the PACU, and on days 1,2, and 3 after surgery or until discharge from hospital (for definition, see Supplementary Table S2). Blood was collected at these sampling points and plasma aliquoted and stored at −80°C until batch analysis. The hs-cTnT was measured by an electrochemiluminescence-immunoassay on a Cobas e602/Cobas e601/Cobas e411 analyser (Roche Diagnostics, Mannheim, Germany). The lower limit of detection for hs-cTnT was 3 ng L^{-1} with a 10% coefficient of variation at 13 ng L^{-1}. The 99th percentile for a normal health population for this assay is 14 ng L^{-1}.

Collection of ECGs, plasma samples, and clinical symptom assessment were conducted by trained research staff outside

Table 1 Characteristics of the study population.

Characteristics		Number with data (%)	Whole population	With primary outcome n=124	Without primary outcome n=1167
Age (yr, IQR)		1291 (100)	70 (63–76)	73.5 (68–78)	70 (63–76)
Sex, female, n (%)		1291 (100)	592 (45.9)	40 (32.3)	552 (47.3)
Comorbidities, n (%)	Coronary artery disease	1291 (100)	168 (13.0)	34 (27.4)	134 (11.5)
	Heart failure	1291 (100)	69 (5.3)	18 (14.5)	51 (4.4)
	Atrial fibrillation	1291 (100)	123 (9.5)	20 (16.1)	103 (8.8)
	Hypertension	1289 (99.8)	636 (49.3)	64 (51.6)	572 (49.1)
	Stroke or TIA	1291 (100)	107 (8.3)	13 (10.5)	94 (8.1)
	IDDM	1290 (99.9)	101 (7.8)	12 (9.7)	89 (7.6)
	Hyperlipidaemia	1290 (99.9)	217 (16.8)	16 (12.9)	201 (17.2)
	COPD	1291 (100)	169 (13.1)	19 (15.3)	150 (12.9)
	Liver cirrhosis	1291 (100)	7 (0.5)	1 (0.8)	6 (0.5)
	Chronic kidney disease	1291 (100)	15 (1.2)	3 (2.4)	12 (1.0)
	Metastatic cancer	1290 (99.9)	163 (12.6)	15 (12.1)	148 (12.7)
RCRI (no. of risk factors) n (%)	1	1291 (100)	929 (72.0)	68 (54.8)	861 (73.8)
	2		278 (21.5)	36 (29.0)	242 (20.7)
	≥3		84 (6.5)	20 (16.1)	64 (5.5)
ASA physical status, n (%)	1	1291 (100)	157 (12.2)	10 (8.1)	147 (12.6)
	2		726 (56.2)	52 (41.9)	674 (57.8)
	3		399 (30.9)	58 (46.8)	341 (29.2)
	4		9 (0.7)	4 (3.2)	5 (0.4)
MET, n (%)	<1	1290 (99.9)	45 (3.5)	7 (5.7)	38 (3.3)
	1–4		618 (47.9)	66 (53.2)	552 (47.3)
	≥4		627 (48.6)	51 (41.1)	576 (49.4)
Preoperative medications, n (%)	Platelet inhibitors	1289 (99.8)	191 (14.8)	27 (21.8)	164 (14.1)
	Statins	1290 (99.9)	345 (26.7)	38 (30.6)	307 (26.3)
	B-blockers	1289 (99.8)	366 (28.4)	51 (41.1)	315 (27.0)
	Ca-channel inhibitors	1288 (99.8)	222 (17.2)	21 (16.9)	201 (17.3)
	ACEi or ARBs	1289 (99.8)	446 (34.6)	42 (33.9)	404 (34.7)
Surgical category, n (%)	Upper gastrointestinal	1289 (99.8)	109 (8.5)	17 (13.7)	92 (7.9)
	Hepatobiliary		242 (18.8)	18 (14.5)	224 (19.2)
	Pancreas		193 (15.0)	27 (21.8)	166 (14.2)
	Colorectal		466 (36.2)	36 (29.0)	430 (36.9)
	Urology (not renal)		68 (5.3)	4 (3.2)	64 (5.5)
	Renal		118 (9.2)	9 (7.3)	109 (9.4)
	Gynaecology		72 (5.6)	9 (7.3)	63 (5.4)
	Other		21 (1.63)	4 (3.23)	17 (1.46)
Preoperative anaemia, n (%)	Male <130 g L^{-1}, Female <120 g L^{-1}	1286 (99.6)	522 (40.6)	73 (59.3)	449 (38.6)
Preoperative increased creatinine, n (%)	Male ≥100 μmol L^{-1}, Female ≥90 μmol L^{-1}	1272 (98.5)	216 (17.0)	30 (24.8)	186 (16.2)
Duration of surgery, n (%)	Mean (SD), h	1289 (99.8)	4.11 (2.54)	4.69 (2.83)	4.05 (2.50)
Intraoperative blood loss, n (%)	Median (IQR) (ml)	1288 (99.8)	150 (50–400)	300 (100–500)	150 (50–400)
Intraoperative transfusion, n (%)		1289 (99.8)	145 (11.2)	23 (18.5)	122 (10.5)
Intraoperative hypotension, n (%)	MAP ≤55 mm Hg at any time	1286 (99.6)	675 (52.5)	656 (52.4)	610 (52.5)
Discharge destination, n (%)	PACU	1290 (99.9)	1259 (97.6)	113 (91.1)	1146 (98.3)
	ICU (planned)		13 (1.0)	5 (4.0)	8 (0.7)
	ICU (unplanned)		18 (1.40)	6 (4.8)	12 (1.0)
Ischaemic symptoms*, n (%)	PACU-30 d	1289 (99.8)	148 (11.5)	46 (37.1)	102 (8.8)
Ischaemic ECG, n (%)	PACU-30 d	1280 (99.1)	269 (21.0)	42 (34.7)	227 (19.6)
Ischaemic symptom *or* ECG, n (%)	PACU-30 d	1281 (99.2)	385 (30.1)	65 (52.8)	320 (27.6)
30-Day MACCE, n (%)		1291 (100)	120 (9.3)	120 (96.8)	0 (0)
30-Day mortality, n (%)		1291 (100)	14 (1.1)	14 (11.3)	0 (0)
30-Day MACCE, mortality, or both, n (%)		1291 (100)	124 (9.6)	124 (100)	0 (0)

ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; IDDM, insulin-dependent diabetes mellitus; IQR, inter-quartile range; MACCE, major adverse cardiovascular and cerebrovascular events; MET, metabolic equivalents; MINS, myocardial injury in noncardiac surgery; RCRI=Revised Cardiac Risk Index; SD, standard deviation; TIA, transient ischaemic attack.
* Postoperatively, suggestive of ischaemia.

of routine care. In order to mitigate the risk of detection and reporting bias, these were collected, analysed, and interpreted blindly. Plasma samples were analysed in batch by a central laboratory without knowledge of clinical status and ECG findings, and clinical data were collected without knowledge of ECG and hs-cTnT findings. Treating teams were not given access to these non-routine investigations. However, routine care may have included the measurement of hs-cTnT and ECGs, and these results were not available to study assessors. Data entry into a centralised General Data Protection Regulation-compliant secure electronic database was conducted by investigators at each site and validated by the study coordinators.

The primary outcome was the composite of all-cause mortality and MACCE at 30 days after surgery. MACCE was defined as non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina, stroke, or any combination of these (Supplementary Table S3).[19]

Statistical analysis

Sample size was calculated assuming a prevalence of elevated hs-cTnT of 10% with an estimated incidence of the primary outcome of 6.8% in the non-elevated hs-cTnT group.[2,19] The calculation was powered to detect a relative difference of 10% between elevated and non-elevated hs-cTnT groups, for both primary and secondary (1 yr mortality) outcomes. Secondary outcomes are not presented in this study. The largest calculated sample size was 1142. Sample size was increased to 1600 patients to account for a missing data rate of 33%. On June 18, 2019, interim data were submitted (716 patients) to an independent Data Safety and Monitoring Board (DSMB). Since the frequencies of the outcomes were in line with original expectations and the missing data rate was low, the DSMB allowed a sample size revision to 1269 patients. This sample size also allowed for adjustment of 10 independent factors in a multivariable analysis, assuming an event rate of 8% in the whole population. Patients with missing preoperative hs-cTnT or without at least one postoperative hs-cTnT measurement and those with missing follow-up at 30 days were not included in the analysis.

Summary statistics are presented as mean (standard deviation), median [inter-quartile range (IQR)], or number (%). The magnitude of the exposure effect estimate was reported as an adjusted odds ratio (OR) with 95% confidence intervals (CI). P-values were two-sided with a significance level of 5%. We used the χ^2 test to compare patients with or without the primary outcome. Analyses were conducted using Stata Statistical Software, StataCorp, College Station, Texas, Release 14.

Receiver operating characteristic (ROC) analysis was conducted to identify the optimal cut-off concentrations for preoperative levels and perioperative increases (peak postoperative minus preoperative value) in hs-cTnT, defined according to Youdens J-index for best discrimination of the primary outcome. For each hs-cTnT threshold we summarised sensitivity, specificity, and positive and negative predictive values (Supplementary Table S4).

We investigated four thresholds for perioperative myocardial injury: 1) preoperative hs-cTnT defined by ROC analysis, 2) perioperative increase defined by the Basel-PMI study,[3] (i.e. an increase in perioperative hs-cTnT of $\geq$14 ng L^{-1} above preoperative values), 3) perioperative change defined by the VISION study,[2] (i.e. a postoperative concentration 20 to <65 ng L^{-1} with an absolute change of $\geq$5 ng L^{-1} or a postoperative concentration of $\geq$65 ng L^{-1}), and 4) perioperative increase defined by ROC analysis. Peak postoperative values regardless of the day of sampling were used in these calculations.

Univariable analyses were conducted to identify possible associations between a priori defined predictor variables and the primary outcome and multivariable logistic regression was applied to test their independent associations. Predictor variables were chosen based on clinical plausibility and previous evidence and entered into the final model using backward stepwise elimination. Collinearity was assessed using the variance inflation factor (VIF), and only variables with VIFs $\leq$10 were entered into the models.

Model performance was assessed using ROC analyses with the probability of the outcome calculated from the logistic regression analysis. Discrimination of the model was reported as the c-index. Overall calibration and goodness of fit was assessed with the Hosmer−Lemeshow test, plots of predicted vs observed probabilities of the outcome, and the Akaike Information Criterion (AIC, lower scores indicate better fit). The Brier score was used to indicate accuracy of prediction. Net reclassification indices (NCIs) for each of the four hs-cTnT thresholds were calculated (Supplementary Table S5).

To explore the value of adding perioperative hs-cTnT to the RCRI, the weighted comparison (WC) net benefit method[20] was used, which takes into account the prevalence of outcome. 'Extended RCRI' was calculated by adding +1 to the RCRI score, when the hs-cTnT test was 'positive' as defined by the various thresholds. Because all patients in this study had an RCRI score of $\geq$1 (major surgery), an extended RCRI score $\geq$2 was considered 'test positive'. WC for the extended RCRI compared with RCRI alone were calculated as:

$$\Delta \text{Sensitivity} + [(1\text{-prevalence/prevalence}) \times \text{clinical threshold} \times \Delta \text{Specificity}]$$

where

ΔSensitivity=Sensitivity$_{\text{'extended RCRI'}}$−Sensitivity$_{\text{RCRI alone}}$
and
ΔSpecificity=Specificity$_{\text{'extended RCRI'}}$−Specificity$_{\text{RCRI alone}}$

The clinical threshold is the ratio of true positives to false positives (TP:FP). Thus, the WC method weights differences in sensitivity and specificity by a trade-off of acceptable clinical TP:FP ratios, and takes into account disease prevalence. Positive WC values indicate a net benefit and negative values indicate a net loss. We extended the WC method by constructing WC curves to aid clinicians in making informed choices regarding the net benefit of measuring hs-cTnT in this population across a range of clinical thresholds.

Two sensitivity analyses were conducted. The first was restricted to patients with preoperative creatinine within the normal range reported for Swedish laboratories (male $\leq$100 μmol L^{-1}, female $\leq$90 μmol L^{-1}); in the second analysis, patients with increased perioperative troponins attributable to non-ischaemic causes (e.g. pulmonary emboli, sepsis) were excluded.

The four hs-cTnT thresholds obtained in our population were externally validated in an independent population consisting of 271 patients undergoing major abdominal surgery at the University Hospital Basel, Switzerland. Although the same inclusion and outcome criteria were applied in both

populations, the Basel cohort was retrospective and consisted entirely of patients with or at risk of cardiovascular disease. Also, hs-cTnT was measured within 30 days before surgery and on postoperative days 1 and 2, according to perioperative routine in Basel. We calculated sensitivities, specificities, positive predictive value (PPV), negative predictive value (NPV), and the c-statistics for the different hs-cTnT thresholds in this population. Finally, we applied logistic regression analysis to calculate the ORs for 30-day mortality and MACCE in this external cohort.

Results

A total of 1368 patients were recruited to the study, 1291of whom were included in the final analysis (Fig. 1). Population characteristics are shown in Table 1. The primary outcome occurred in 9.6% (124 patients) of patients, with a mortality rate of 1.1% (14 patients) and MACCE of 9.3% (120 patients). The missing data rate was very low (~1%, Table 1). Preoperative and at least one postoperative hsTnT measurement was available for all patients. Peak hs-cTnT levels occurred on Day 2 (median 12.1 ng L^{-1}, IQR 8.2−19.9).

We performed ROC analyses to identify the best thresholds in hs-cTnT when measured preoperatively or as perioperative change (peak postoperative-preoperative value). The ROC analysis identified that a preoperative hs-cTnT of $\geq$14 ng L^{-1} (area under the ROC curve [AUC] 0.64, CI 0.58−0.69) and a perioperative increase in hs-cTnT of $\geq$5 ng L^{-1} (AUC 0.67, CI 0.62−0.72) provided best discriminatory values for the primary outcome. The incidence of MACCE and all-cause mortality at 30 days after surgery stratified by the two hs-cTnT thresholds and two previously published thresholds for myocardial injury (Basel-PMI study and VISION study) are shown in Table 2. Sensitivities, specificities, and positive and negative predictive values for all four hs-cTnT thresholds are provided in

Supplementary Table S4, and their NCIs are reported in Supplementary Table S5.

Univariable analyses were applied to investigate the association of the four thresholds and *a priori* defined predictor variables with the primary outcome (Supplementary Table S6). Patient age, sex, ASA physical status, cardiovascular medications, comorbidities, preoperative anaemia, preoperative increased creatinine, surgical category, intraoperative transfusion, length of surgery, RCRI, and hs-cTnT were associated with 30-day MACCE and all-cause mortality.

We tested the independent association of the pre- and perioperative increases in hs-cTnT with the primary outcome using multivariable regression (Table 3). Performance statistics are given in Table 4 and calibration plots are provided in Supplementary Figure S1. The Basel-PMI definition (perioperative increase $\geq$14 ng L^{-1} above preoperative value) had the highest prediction accuracy (Brier 0.080), provided the best fit among the four tested models (AIC 746) and was associated with the highest adjusted OR for the primary outcome, thus we considered this to be statistically optimal among the four thresholds tested.

The majority of myocardial injuries were detected by Day 2 postoperatively (Table 5), and 1281 (99.2%) of all patients did not have ischaemic symptoms. For hs-cTnT, there were 1250 PACU measurements and 1244 Day 1 measurements, 1102 Day 2 measurements, and 816 Day 3 measurements; and a total of 752 patients had measurement for all five sampling points. The majority of unavailable hs-cTnT data for days 2 and 3 were as a result of discharge. Although all 1291 patients fulfilled our prespecified criteria of a preoperative and at least one postoperative hsTnT measurement for inclusion in the study, we cannot exclude that the true incidence of myocardial injury may have been underestimated. Preoperative increased hsTnT was detected in 349 (27%) and perioperative increases in 11.2−34.2% depending on the threshold used.
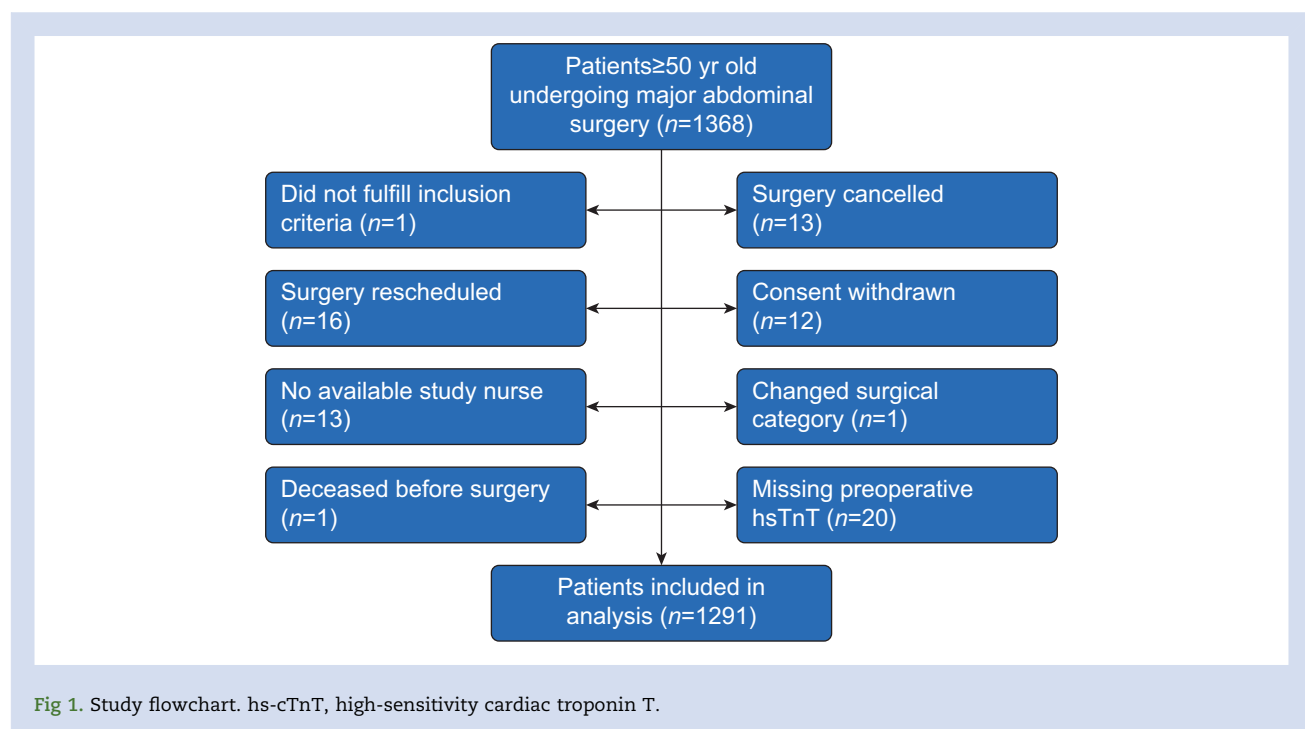

Fig 1. Study flowchart. hs-cTnT, high-sensitivity cardiac troponin T.

Table 2 30-Day MACCE and all-cause mortality in the whole population and stratified according to various high-sensitivity cardiac troponin T (hs-cTnT) thresholds.

Definition	Whole population (n=1291)	Preoperative (ROC analysis) According to ROC analysis; ≥14 ng L⁻¹			Perioperative increase (Basel-PMI) Perioperative increase ≥14 ng L⁻¹ above preoperative value			Perioperative change (VISION) 20 to <65 ng L⁻¹ AND a change of ≥5 ng L⁻¹ or any postoperative value ≥65 ng L⁻¹			Perioperative increase (ROC analysis) Perioperative increase (≥5 ng L⁻¹ above preoperative value)		
		With increase (n=349)	Without increase (n=942)	P-value	With increase (n=144)	Without increase (n=1147)	P-value	With increase (n=357)	Without increase (n=934)	P-value	With increase (n=442)	Without increase (n=849)	P-value
30-Day mortality+MACCE, n (%)	124 (9.6%)	61 (17.5%)	63 (6.7%)	<0.0001	36 (25.0%)	88 (7.7%)	<0.0001	69 (19.3%)	55 (5.9%)	<0.0001	72 (16.3%)	52 (6.1%)	<0.0001
30 Day MACCE, n (%)	120 (9.3%)	60 (17.2%)	60 (6.4%)	<0.0001	36 (25.0%)	84 (7.3%)	<0.0001	68 (19.0%)	52 (5.6%)	<0.0001	71 (16.1%)	49 (5.8%)	<0.0001

MACCE, major adverse cardiovascular and cerebrovascular events; ROC, receiver operating characteristic.

Sensitivity analyses

In order to evaluate the effect of preoperative renal dysfunction, we restricted the multivariable model to patients without preoperative creatinine increases (Supplementary Table S7). We further evaluated the independent association between hs-cTnT and the primary outcome excluding patients with non-ischemic causes of troponin elevation (e.g. sepsis and pulmonary embolus) (Supplementary Table S8). Both analyses confirmed the results of the primary model.

Net benefit of hs-cTnT beyond RCRI

WCs were calculated and plotted across a range of clinical thresholds (Fig. 2). Extrapolation of all WC curves shows that measurement of perioperative hs-cTnT changes was associated with a net benefit compared with RCRI alone for clinical thresholds <0.29, corresponding to >3.4 false positives for each true positive. At clinical thresholds ≥0.18 (≤5.6 false positives for each true positive), the Basel-PMI definition provided the best net benefit. At clinical thresholds between 0.18 and 0.03 (5.6−33.3 false positives for each true positive) the VISION definition provided the best net benefit. At clinical thresholds ≤0.03 (≥33.3 false positives for each true positive) the definition determined by ROC analysis in this population provided the best net benefit.

External validation

We externally validated the hs-cTnT thresholds in an independent population (n=271). Population characteristics for this independent cohort are shown in Supplementary Table S9. OR and performance characteristics of the different hs-cTnT thresholds are shown in Supplementary Table S10. The OR for the primary outcome was highest when applying a threshold of perioperative increase in hs-cTnT of ≥14 ng L⁻¹, even after adjustment for RCRI and other factors (adjusted OR 11.2, 95% CI 4.9−25.5).

Discussion

An increase in hs-cTnT ≥14 ng L⁻¹ above preoperative values identified acute perioperative myocardial injury with the highest risk estimates for the primary outcome and provided a net benefit across a wide range of clinical thresholds.

All four thresholds for acute perioperative myocardial injury were independently associated with 30-day MACCE and all-cause mortality. When model performance was assessed using c-statistics, Brier scores, and the AIC, the model incorporating the Basel-PMI threshold provided best performance characteristics, although the differences were modest. In a multivariable model, patients with elevated hs-cTnT before surgery were at increased risk of the primary outcome, and this risk was amplified if hs-cTnT was elevated further. Further, the model with the Basel-PMI threshold provided highest adjusted OR for mortality and MACCE, a finding confirmed in the external validation cohort and sensitivity analyses. The WCs analysis demonstrated that all tested thresholds for perioperative myocardial injury provided a net benefit over RCRI alone. However, the model using a dynamic change in hs-cTnT, with increases ≥14 ng L⁻¹ above preoperative values performed best.

Our findings add to previous studies that often do not take into account RCRI, ASA physical status, preoperative anaemia,

Table 3 Multivariable analysis with and without the four different hs-cTnT thresholds.

Variable	Without hs-cTnT but including RCRI OR (CI)	P-value	Preoperative (ROC analysis) OR (CI)	P-value	Perioperative increase (Basel-PMI) OR (CI)	P-value	Perioperative change (VISION) OR (CI)	P-value	Perioperative increase (ROC analysis) OR (CI)	P-value
Patient age	1.0 (1.0–1.1)	0.038	1.0 (0.99–1.1)	0.156	1.0 (1.0–1.1)	0.040	1.0 (0.99–1.0)	0.211	1.0 (1.0–1.1)	0.108
Sex	1.5 (1.0–2.3)	0.049	1.4 (0.92–2.2)	0.114	1.4 (0.92–2.2)	0.116	1.3 (0.87–2.1)	0.184	1.4 (0.93–2.2)	0.103
ASA physical status	1.7 (1.0–2.7)	0.034	1.6 (0.97–2.5)	0.069	1.6 (1.0–2.6)	0.048	1.5 (0.92–2.4)	0.111	1.6 (0.98–2.5)	0.062
MET	0.93 (0.6–1.4)	0.728	0.93 (0.61–1.4)	0.753	0.9 (0.61–1.4)	0.762	0.96 (0.63–1.5)	0.867	0.92 (0.60–1.4)	0.684
No. of chronic comorbidities				0.158		0.212		0.179		0.234
1	1.0 (0.6–1.8)	0.976	1.0 (0.57–1.8)	0.995	0.99 (0.56–1.7)	0.958	0.98 (0.56–1.7)	0.948	0.97 (0.56–1.7)	0.924
2	0.80 (0.41–1.6)	0.505	0.80 (0.41–1.6)	0.505	0.73 (0.37–1.5)	0.366	0.76 (0.38–1.5)	0.420	0.72 (0.36–1.4)	0.348
≥3	0.44 (0.18–1.1)	0.064	0.42 (0.17–1.0)	0.049	0.43 (0.18–1.0)	0.058	0.42 (0.17–1.0)	0.050	0.43 (0.18–1.0)	0.062
Preoperative anaemia*	1.6 (1.1–2.5)	0.020	1.5 (1.0–2.3)	0.052	1.6 (1.0–2.4)	0.040	1.5 (0.95–2.2)	0.085	1.6 (1.0–2.4)	0.032
Preoperative increased P-creatinine†	1.2 (0.77–2.0)	0.380	1.1 (0.70–1.9)	0.588	1.2 (0.75–2.0)	0.414	1.0 (0.62–1.7)	0.936	1.1 (0.66–1.8)	0.768
Intraoperative transfusion‡	1.2 (0.68–2.0)	0.553	1.1 (0.66–2.0)	0.633	1.1 (0.64–2.0)	0.684	1.1 (0.64–1.9)	0.722	1.1 (0.63–1.9)	0.738
Intraoperative hypotension§	0.98 (0.66–1.5)	0.911	0.99 (0.67–1.5)	0.958	0.91 (0.61–1.4)	0.630	0.99 (0.66–1.5)	0.942	0.93 (0.62–1.4)	0.715
Length of surgery (min)	1.1 (1.0–1.2)	0.007	1.1 (1.0–1.2)	0.007	1.1 (1.0–1.2)	0.020	1.1 (1.0–1.2)	0.016	1.1 (1.0–1.2)	0.029
RCRI				0.013		0.017		0.014		0.013
2 Risk factors	1.8 (0.97–3.2)	0.063	1.8 (0.98–3.2)	0.058	1.8 (0.95–3.2)	0.070	1.8 (0.97–3.2)	0.063	1.8 (0.97–3.2)	0.064
≥3 Risk factors	3.9 (1.6–9.4)	0.002	3.8 (1.6–9.1)	0.003	3.7 (1.5–9.0)	0.004	3.7 (1.5–9.1)	0.004	3.8 (1.6–9.2)	0.003
Change in hs-cTnT	—	—	1.7 (1.0–2.6)	0.035	2.9 (1.8–4.7)	<0.001	2.4 (1.5–3.7)	<0.001	2.2 (1.4–3.3)	<0.001

ASA, American Society of Anesthesiologists; CI, confidence interval; hs-cTnT, high-sensitivity troponin T; MET, metabolic equivalents; OR, odds ratio; RCRI, Revised Cardiac Risk Index; ROC, receiver operating characteristic.
* Defined as haemoglobin <130 g L^{-1} for men and <120 g L^{-1} for women.
† Defined as plasma levels of creatinine ≥100 µmol L^{-1} for men and ≥90 µmol L^{-1} for women.
‡ Defined as intraoperative transfusion of any blood product.
§ Defined as MAP ≤55 mm Hg at any time intraoperatively.

intraoperative transfusion, intraoperative hypotension, and length of surgery, which are known risk factors for poor perioperative outcomes.[10,11,21–28] The independent association between hs-cTnT and the primary outcome was confirmed by sensitivity analyses excluding patients with pre-existing renal dysfunction and noncardiac causes of hs-cTnT increases (e.g. sepsis and pulmonary emboli). Preoperative anaemia, the presence of three or more comorbidities, length of surgery, RCRI, and hs-cTnT were the most important risk factors for 30-day mortality and MACCE.

Our study highlights the presence of modifiable risk factors such as preoperative anaemia and length of surgery, where targeted management may improve outcomes. We provide support for the value of enhanced preoperative risk stratification with the addition of hsTnT to the RCRI to identify a group of very high-risk patients.[12,13] While no evidence-based guidance exists to support any preoperative strategy to improve outcomes in such a risk group, identification of increased risk may provide incentives for meticulous perioperative management, such as patient blood management, increased haemodynamic monitoring, increased postoperative monitoring, and optimisation of cardiovascular medications.

The strength of association with the primary outcome was most marked when perioperative changes in hs-cTnT are considered, and preoperative measurements alone do not provide information on acute perioperative events. Thus, our results support the measurement of perioperative hs-cTnT increases, rather than preoperative hs-cTnT alone. These findings are congruent with an earlier study that demonstrated a stepwise increase in risk of adverse cardiovascular events when perioperative changes occur in addition to increased preoperative hsTnT levels.[3]

Ambiguity regarding appropriate cut-off values for defining acute perioperative myocardial injury has led to considerable difficulty in evaluating the utility of hs-cTnT in perioperative

Table 4 Performance statistics for the four models including different thresholds of hs-cTnT and for a model excluding hs-cTnT.

hsTnT threshold	Definition	AUC (95% CI)		Brier score	Hosmer–Lemeshow		AIC
		c-statistic	P-value		χ^2	Prob$\geq\chi^2$	
Preoperative (ROC analysis)	According to ROC analysis; $\geq$14 ng L^{-1}	0.72 (0.68–0.77)	<0.0001	0.082	10.9	0.21	759
Perioperative increase (Basel-PMI)	Perioperative increase $\geq$14 ng L^{-1} above preoperative value	0.73 (0.68–0.78)	<0.0001	0.080	8.9	0.35	746
Perioperative change (VISION)	20 to <65 ng L^{-1} AND a change of $\geq$5 ng L^{-1} or any postoperative value $\geq$65 ng L^{-1}	0.73 (0.69–0.78)	<0.0001	0.081	5.7	0.68	750
Perioperative increase (ROC analysis)	Perioperative increase ($\geq$5 ng L^{-1} above preoperative value)	0.73 (0.68–0.78)	<0.0001	0.081	7.4	0.50	751
No hs-cTnT measurement	—	0.71 (0.66–0.76)	<0.0001	0.082	6.5	0.59	762

Model performance was assessed by a combination of the C-statistic, Brier score (lower values=higher predictive accuracy) and the AIC (lower score-=better model fit).
AIC, Akaike Information Criterion; AUC, area under the receiver operating characteristic curve; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; ROC, receiver operating characteristic.

care. We derived and externally validated two hs-cTnT thresholds based on ROC analysis in the current population, and provide an external validation for two previously published definitions.[2,3] We also make head to head comparisons of four multivariable models that included each of the hs-cTnT thresholds, and a model without hs-cTnT. Although summary statistics such as sensitivity, specificity, NPVs and PPVs, and c-indices are informative, they provide limited value for implementation in clinical practice. Difficulties in determining optimal sensitivity and specificity trade-offs, and lack of a nuanced consideration between clinical benefit vs risk are limitations with these performance statistics. We also note that ROC curves provided only modest values of the c-index, in line with previous studies.[4,12] However, ROC curves do not provide an adequate summary statistic since they combine accuracies across a wide range of thresholds and may not highlight thresholds that are most clinically relevant. Calculation of the NRI may be misleading, since it does not account for disease prevalence. The net absolute reclassification index (NARI) is an adjustment of NRI to include disease prevalence, however true positive classifications are still weighted equally as true negative classifications, which may be unreasonable within the perioperative context where correct classification of true positives may be more meaningful. We assume that most clinicians (and patients) would value missing a life-threatening disease higher than diagnosing a healthy patient as positive.

We used the WC net benefit method[20] to provide an aid to clinical decision-making, since this method takes into account both disease prevalence and TP:FP ratios (clinical threshold). Rather than choosing an arbitrary TP:FP ratio, we plotted the net benefit over a range of clinical thresholds (Fig. 2). All four thresholds, including preoperatively elevated hs-cTnT, demonstrated net benefits compared with RCRI alone when the clinical threshold was <0.29. Perioperative hs-cTnT measurement, when using the Basel-PMI definition, provided a net benefit compared with RCRI alone at clinical thresholds between 0.18 and 0.29. The other definitions also provided a net benefit compared with RCRI alone, but incurred a higher cost in terms of decreased TP:FP ratios. Thus, increased detection of disease should be weighed against increased probability of false positives, and the distress and unnecessary investigations that this may entail. For risk averse clinicians, where many more false positives than true positives are accepted, the net benefit was highest for increased hs-cTnT $\geq$5 ng L^{-1}, that provided a net benefit at clinical thresholds $\leq$0.03. For clinical thresholds >0.29, accepting less than 3.4 false positives to each true positive, there was no net benefit of adding hs-cTnT measurement to the RCRI.

The present results fill a gap in knowledge regarding the utility of cTns in perioperative care. We obtained pre- and postoperative troponin measurements, ECGs, and clinical information regarding ischaemic symptoms in all patients, regardless of clinical indication. Thus, we provide an unbiased indication of the true incidence of acute myocardial infarction, that has been a limitation in previous studies.[2,29,30] The most appropriate thresholds to apply for perioperative hs-cTnT surveillance have not been previously investigated and our study provides an analysis of two previous definitions for perioperative hs-cTnT changes and two data-derived thresholds. The optimal threshold was comprehensively tested by multiple methods and their predictive value identified after

Table 5 Timing of myocardial injury diagnosis, according to the different high-sensitivity cardiac troponin T (hs-cTnT) thresholds.

	PACU (n=1250)	Day 1 (n=1244)	Day 2 (n=1102)	Day 3 (n=816)
Perioperative increase (Basel-PMI), n=144. n(%)	31 (21.5)	51 (35.4)	47 (32.6)	15 (10.4)
Perioperative change (VISION), n=357. n(%)	158 (44.6)	134 (37.9)	52 (14.7)	11 (3.1)
Perioperative increase (ROC analysis), n=442. n(%)	104 (23.5)	189 (42.8)	122 (27.6)	27 (6.1)

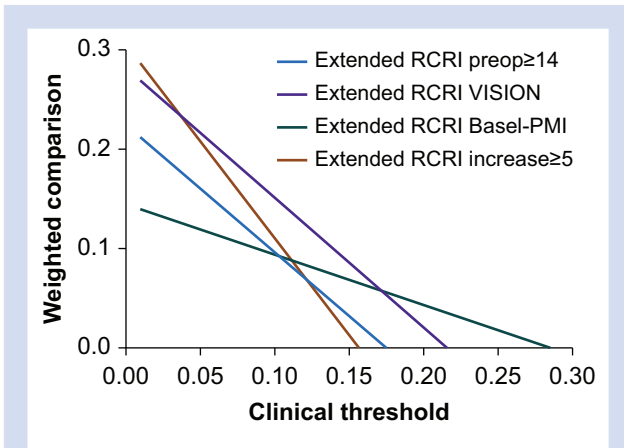ROC, receiver operating characteristic.

Fig 2. Weighted comparison (WC) curves for extended RCRI incorporating each of the hs-cTnT thresholds. The clinical threshold represents the chosen 'acceptable' ratio of true positives to false positives (TP:FP) that may be considered reasonable in a clinical setting. Extended RCRI=RCRI score +1 when the hs-cTnT test was 'positive' according to the four thresholds: preoperative ≥ 14 ng L^{-1} (ROC analysis), VISION definition, Basel-PMI definition and perioperative increase ≥ 5 ng L^{-1} (ROC analysis). Positive WC values indicate a net benefit for extended RCRI compared with RCRI alone. hs-cTnT, high-sensitivity cardiac troponin T; RCRI, Revised Cardiac Risk Index; ROC, receiver operating characteristic.

careful adjustment for pre- and perioperative risk factors. Further, our findings were externally validated. We present evidence for the use of acute perioperative hs-cTnT changes, rather than pre- or postoperative measurements alone, in line with the recently published recommendations of the StEP COMPAC: cardiovascular outcomes initiative.[30] A decision analysis is provided to help clinicians consider the risk and benefits of hsTnT measurements across a wide range of clinical thresholds. We suggest that hsTnT measurements may be used as a two-step risk management process: a first step with preoperative hsTnT measurement for the identification of high-risk patients beyond the RCRI, that may be subject to enhanced perioperative management strategies; a second step with perioperative hsTnT changes for the early detection of myocardial injury.

The implementation of hs-cTnT surveillance is costly and many clinicians argue that this may be futile in the absence of evidence-based guidelines for management. However, we argue that clinically accepted risk stratification tools, such as the RCRI, are also not coupled to specific perioperative management strategies. Recent studies suggest that myocardial injury in noncardiac surgery (MINS) is amenable to treatment.[31–33] In order to minimise the cost and inconvenience of blood sampling, our data suggest that a minimum of three measurements, taken preoperatively and on days 1 and 2 postoperatively (earlier if the patient is discharged), would detect the majority of myocardial injuries. Measurement of both pre- and postoperative hs-cTnT will also differentiate between acute and chronic myocardial injury, consistent with the recommendation of the consensus statement issued by the Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction.[34]

Several limitations of this study should be mentioned. Firstly, the findings of this study only apply to hs-cTnT and not troponin I. Although we have included the most important independent variables in the multivariable analysis, the possibility of unadjusted factors remains. None of our patients underwent further cardiac assessments within the context of our study, thus it is not possible to attribute a cause for increased hs-cTnT. Whilst our study provides evidence for hs-cTnT surveillance, we stress that net benefit is highly dependent on clinically acceptable levels of TP:FP ratios. Although hs-cTnT screening will detect perioperative myocardial injury, only one in 4.4 patients will develop MACCE or die within 30 days of surgery when using the best-performing of the evaluated hs-cTnT thresholds in addition to the RCRI.

This is especially important when considering future management of patients with increased perioperative hs-cTnT. In MANAGE, the only trial investigating treatment of patients with MINS, dabigatran reduced the risk of major vascular complications without increasing the risk of major bleeding.[31] However, the hs-cTnT criterion for defining MINS was an absolute change of at least 5 ng L^{-1} between any two (mostly postoperative) measurements. Whether the application of the thresholds defined in the present study may more adequately select patients at increased risk, and whether this translates to better post-interventional outcomes, would be relevant questions for future research. Finally, there is still no consensus on management of patients with perioperative myocardial injury.

Conclusions

An increase in hs-cTnT ≥ 14 ng L^{-1} above preoperative values identified acute perioperative myocardial injury and was independently associated with 30-day all-cause mortality and MACCE. Perioperative hs-cTnT surveillance provided a net benefit over RCRI for the identification of patients at high risk of death and MACCE.

Authors' contributions

Acknowledgements

Declarations of interest

Funding

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.10.006.

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Handling editor: Paul Myles