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N-terminal proBNP adds prognostic value to high-sensitivity cardiac troponin I in elective thoracic surgery: an observational cohort study

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ABSTRACT

Background Perioperative myocardial injury (PMI) is a common complication following non-cardiac, particularly thoracic, surgery and is associated with increased cardiovascular risk. Although guidelines recommend cardiac biomarker monitoring to detect PMI, its implementation in routine clinical practice remains limited.

Objective To evaluate the combined use of high-sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in predicting major adverse cardiovascular events (MACE) following elective thoracic surgery, and to determine whether NT-proBNP provides incremental prognostic value beyond hs-cTnI alone.

Design Multicentre observational cohort study.

Setting Conducted between February 2021 and November 2023 in three Spanish tertiary hospitals.

Participants Patients aged ≥45 years scheduled for elective thoracic surgery involving lung resection (pneumonectomy, lobectomy, bilobectomy or segmentectomy) under general anaesthesia. Exclusion criteria included urgent or non-thoracic surgery, active infection or sepsis and a history of severe heart failure (ejection fraction <30%).

Main outcome measures Combined measurement of hs-cTnI and NT-proBNP at baseline (preoperatively) and at 24 and 48 hours postoperatively.

PMI was defined as hs-cTnI ≥45 ng/L at 24 and/or 48 hours or a ≥20% increase from baseline in patients with elevated preoperative concentrations.

Results Among 475 patients, PMI occurred in 11.8%. PMI had higher rates of prior stroke (12.5% vs 2.9%; p=0.004), smoking history (85.7% vs 64.0%; p=0.001) and severe renal dysfunction (7.1% vs 0.7%; p=0.001), with similar Revised Cardiac Risk Index distribution. Patients with PMI also had greater postoperative elevations of hs-cTnI and NT-proBNP (p<0.001), longer surgeries (3.5 hours vs 2.7 hours; p<0.001) and more frequent lobectomy/bilobectomy (64.3% vs 50.4%; p<0.001). Robotic-assisted thoracic surgery (RATS) was associated with increased PMI risk (OR 2.29; p=0.019). Among 49 patients (10.3%) with dual postoperative elevation of hs-cTnI and NT-proBNP, cardiovascular comorbidities were common (hypertension 81.6%, smoking history 85.7%, stroke 14.3%), and most procedures were minimally invasive (video-assisted thoracic surgery 61.2%, RATS 24.5%), with a median duration of 3 hours 42 min. MACE occurred in 18.4% of this group, indicating a substantially elevated risk than isolated or no biomarker elevations. At 30 days, patients with PMI had higher MACE (14.3% vs 3.3%; p<0.001), mortality (3.6% vs 0.7%; p=0.049) and new-onset arrhythmias (5.3% vs 0.2%; p<0.001), particularly atrial fibrillation (7.1% vs 1.7%; p=0.011). Dual biomarker elevation was associated with the highest MACE risk (15.2%), representing a twofold to threefold increase over single biomarkers.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Dual biomarker assessment, including identification of a high-risk dual biomarker subgroup, provided novel insights into perioperative cardiovascular risk and improved prediction of major adverse cardiovascular events (MACE) beyond traditional risk factors.

⇒ The use of high-sensitivity cardiac troponin I (hs-cTnI) assays with rigorous quality control and serial measurements allowed accurate detection of perioperative myocardial injury (PMI) and sustained postoperative cardiac stress.

⇒ Focused on thoracic surgery, this study provides valuable data on a clinically relevant but underrepresented patient population, highlighting the role of surgical factors and comorbidities influencing PMI and MACE.

⇒ Use of predetermined hs-cTnI and N-terminal pro-brain natriuretic peptide cut-offs without adjustment for age or sex, combined with incomplete 48-hour sampling due to early discharge, may have reduced the precision of risk stratification.

⇒ Exclusion of urgent/emergency surgeries and patients with severe heart failure, together with a relatively small sample size, may limit the applicability of findings to patients at highest perioperative risk.

Conclusions Combined hs-cTnI and NT-proBNP assessment improves perioperative cardiovascular risk stratification beyond ischaemia.
Trial registration number NCT04749212

INTRODUCTION

Postoperative mortality accounts for nearly 8% of global deaths, with rates around 2% in patients >45 undergoing non-cardiac surgery.[1 2] As surgeries rise in older, multimorbid populations, early detection of complications is crucial to reduce morbidity and mortality. Cardiovascular complications remain a leading cause of postoperative morbimortality, with perioperative myocardial injury (PMI) being common yet frequently silent, strongly linked to increased mortality.[3 4] Many PMI cases likely go unnoticed due to asymptomatic presentation and the absence of systematic cardiac biomarker monitoring.[5 6] Given recent evidence that PMI is a major contributor to major adverse cardiovascular events (MACE), cardiology and anaesthesiology societies acknowledge that postoperative measurement of high-sensitivity cardiac troponin (hs-cTn) may help identify patients at higher risk, rather than relying solely on clinical signs.[7 8] While routine preoperative biomarker testing to guide management is not currently supported by evidence, observational studies and recent meta-analyses indicate that elevated postoperative hs-cTn concentrations are associated with increased risk of MACE and 30-day mortality.[9–11]

PMI is of particular concern in thoracic surgery, which carries higher cardiovascular stress.[12 13] Procedures involving the lungs, oesophagus and mediastinum may induce PMI via ischaemia-reperfusion, systemic inflammation and haemodynamic shifts.[13]

In patients with known cardiovascular disease or cardiovascular risk factors (including aged ≥65 years) undergoing intermediate-risk or high-risk non-cardiac surgery, the 2022 European Society of Cardiology (ESC) guidelines[8] recommend measuring hs-cTn before surgery and at 24 and 48 hours postoperatively to facilitate risk stratification and detect PMI. The most recent European Society of Anaesthesiology and Intensive Care (ESAIC)-focused guideline[7] also addresses the use of preoperative and postoperative troponin measurements as a prognostic tool, although with weaker evidence and recommendations. More recent guidelines assign a greater role to brain natriuretic peptides (BNP) than to troponin as risk predictors in high-risk non-cardiac surgery patients.[14]

The ESC and ESAIC therefore advise hs-cTn assessment preoperatively and at 24 and 48 hours postoperatively in patients ≥65 or those with cardiovascular risk undergoing intermediate/high-risk surgery.[7 8] However, routine surveillance in thoracic procedures remains inconsistent despite significant underdiagnosis.[8 15] Unlike myocardial infarction (MI), PMI lacks a universal definition, leading to variability in biomarker thresholds. The initial Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) studies coined 'MINS' for myocardial injury without MI criteria, measured only postoperatively.[2] The BASEL-PMI study later combined preoperative and postoperative hs-cTnT, revealing a 14.8% PMI incidence and 20.6% MACE at 1 year, emphasising the need for continuous monitoring.[5 16]

Beyond troponins, BNPs (N-terminal pro-brain natriuretic peptide (NT-proBNP)) are established in heart failure management[17 18] and increasingly recognised as predictors of long-term postoperative risk.[19 20] In 2519 patients >60 undergoing emergency non-cardiac surgery, elevated preoperative NT-proBNP and cTnI independently predicted MACE, with combined measurement improving prognostic value.[21] In thoracic surgery, NT-proBNP has similarly predicted complications such as atrial fibrillation and myocardial ischaemia.[22–24]

Although hs-cTnI is strongly predictive of MACE, it primarily reflects myocardial necrosis and may not capture broader cardiovascular stress or subclinical heart failure. NT-proBNP, a marker of myocardial stretch and neurohormonal activation, provides complementary prognostic information.

Evidence indicates that combining NT-proBNP with hs-cTnI improves risk stratification, capturing aspects of cardiac stress not identified by troponin alone.[25–27] In the context of thoracic surgery, this combined approach may better identify patients at risk for 30-day MACE.

This study aimed to evaluate the combined predictive value of hs-cTnI and NT-proBNP for predicting MACE in elective thoracic surgery, and to determine whether NT-proBNP provides additional prognostic information beyond hs-cTnI alone.

PATIENTS AND METHODS

Study design and population

This prospective, multicentre, observational cohort study was conducted from February 2021 to November 2023 in three Spanish tertiary hospitals. Patients aged ≥45 years scheduled for elective thoracic lung resection (pneumonectomy, lobectomy, bilobectomy or segmentectomy via open or endoscopic approach) were enrolled after preoperative evaluation and informed consent. Exclusion criteria included urgent/emergent surgery, active infection/sepsis and severe heart failure (ejection fraction <30%). The study was registered at ClinicalTrials.gov (NCT04749212) and adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study procedures

Full study methods, including eligibility criteria and data collection procedures, are described in detail in the previously published protocol.[28] Hs-cTnI and NT-proBNP were measured using the Atellica IM (Siemens Healthineers, Germany) with routine quality control at three timepoints: preoperatively, and at 24 and 48 hours postoperatively, integrated into standard blood draws. PMI was defined as hs-cTnI ≥45 ng/L at 24/48 hours or ≥20% rise if baseline was elevated. MI was diagnosed by the fourth

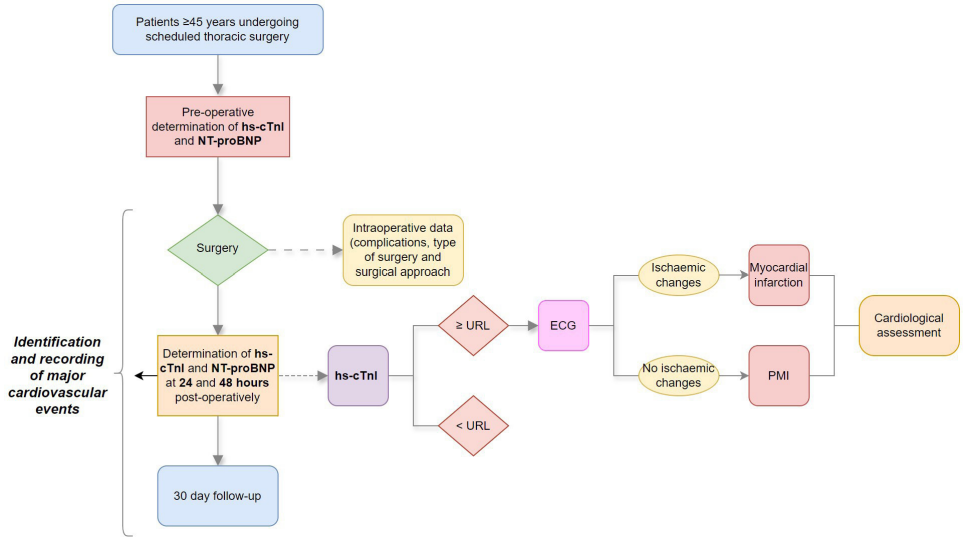

Figure 1 Study procedures. hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; PMI, perioperative myocardial injury; URL, upper reference limit.

universal definition.[29] Abnormal NT-proBNP was defined as ≥125 ng/L preoperatively and ≥300 ng/L postoperatively, reflecting consensus thresholds for stable versus acute settings; age-specific cut-offs were not applied for consistency.[30]

Follow-up and data collection

Patients were monitored in hospital for 2 days postoperatively. ECGs were performed if postoperative hs-cTnI rose or if ischaemic symptoms occurred. Confirmed PMI/MI cases were confirmed by cardiology. At 30 days, telephone follow-up assessed MACE (non-fatal cardiac arrest, MI, heart failure, stroke/transient ischaemic attack, new atrial fibrillation, pulmonary embolism) per guidelines, with events validated by medical records (figure 1). Data were recorded using a secure electronic case report form (*www.clinapsis.com*).

Patient and public involvement

The study was designed and conducted only by the investigators. No patients or members of the public were involved in the design, recruitment, conduct or reporting of the research. Although patient and public involvement is encouraged in all study designs, it was not feasible for this observational study conducted within routine clinical practice.

Outcomes

Our primary outcome was the incidence of all-cause death and MACE during the follow-up according to whether PMI or non-PMI existed; the secondary one was the same for any of the individual MACE components.

Statistical analysis

Sample size was calculated based on previously reported incidences of these biomarkers in similar patient populations. Our group[12] reported a 28% incidence of hs-cTnI elevation, while Cardinale *et al*[22] reported a 22% incidence of NT-proBNP elevation in patients undergoing lung resection. Using these values, we determined that a sample of 310 patients would provide sufficient precision for our primary endpoints, with 95% CIs of 23% to 33% for hs-cTnI and 17.4% to 26.6% for NT-proBNP.[12 22]

To account for potential dropouts, we increased the total planned sample size to 345 patients. This approach allows us to describe biomarker incidences with adequate precision, which is the primary aim of the study. Online supplemental table 1 presents the detailed sample size calculations and precision estimates for both biomarkers.

Data were summarised as mean±SD, median (IQR) or n (%). Continuous variables were expressed as means and SDs or medians and IQRs, while categorical variables as frequencies and percentages.

Comparisons between patients with and without PMI were done with Student's t-test or Mann-Whitney U test for continuous variables, or χ^2 test or Fisher's exact test for categorical variables. ORs with 95% CIs were calculated for all exposure factors. Multivariate logistic regression was performed to identify factors independently associated with PMI, with results expressed as ORs and 95% CIs. Variables entered in the regression model were those with either clinically relevant or statistical significance—or a trend towards it—in univariate analyses. The relationship between postoperative biomarker positivity (ie, elevated hs-cTnI and NT-proBNP) and MACE was checked by χ^2 tests. MACE incidence was described across the four biomarker combinations: both negative, one positive (either marker) or both positive. Analyses were performed using SPSS V.27 (IBM); statistical significance was set at $p<0.05$.

RESULTS

We included 475 patients after excluding those (n=14) not fulfilling inclusion criteria or completing the follow-up.

Baseline characteristics of the patients are presented in table 1, overall and stratified by occurrence of PMI. The mean age was 67.6 years, with slightly over half being male (57.3%).

PMI occurred in 56 patients (11.8% of total). Four patients had preoperative hs-cTnI concentrations >45 ng/L, but only one met PMI criteria in the serial sampling. Most troponin elevations defining PMI occurred within 24 hours (80.6%), and 64.3% remained elevated at 48 hours.

There were few baseline differences between PMI and non-PMI subgroups. Body mass index (BMI) was lower in patients with PMI than in patients without PMI (25.3±3.9 kg/m^2 vs 26.6±4.7 kg/m^2; p=0.02). Most patients had a Revised Cardiac Risk Index (RCRI) class I (84.2%) and class II (13.9%), and index distribution among RCRI classes did not differ between PMI subgroups (p=0.13), indicating broadly comparable perioperative cardiac risk.

Patients with PMI had a higher prevalence of prior stroke (12.5% vs 2.9%; p=0.004) and smoking history (85.7% vs 64.0%; p=0.001), but no differences in other cardiovascular risk factors or diseases. Preoperative haemoglobin and creatinine levels were similar between groups. However, PMI was more frequent (7.1% vs 0.7% in no-PMI) in patients with severe kidney impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), while in remaining eGFR categories (30–44, 45–59 and ≥60 mL/min/1.73 m^2) PMI incidences were broadly comparable between groups, and most PMI cases (48 of 56 cases) occurred in patients with eGFR >60 mL/min/1.73 m^2. Notably, no patients with abnormal eGFR had elevated baseline hs-cTnI. Most patients were in sinus rhythm before surgery (92.2%), with no group differences.

Table 2 shows preoperative and postoperative data of cardiac biomarkers. Preoperatively, median overall hs-cTnI concentration was 3.3 ng/L (3.0–6.0); patients with PMI had a higher median (4.7 ng/L (3.0–7.0)) than those without PMI (3.1 ng/L (2.9–5.8); p=0.005). Elevated preoperative concentrations were observed only in one (1.8%) patient with PMI and three (0.8%) patients without PMI, without differences. The preoperative overall median NT-proBNP concentration was 110 ng/L (59–228), without significant differences between patients with and without PMI (132 ng/L (73–281) vs 108 ng/L (56–222)). Elevated baseline NT-proBNP concentrations were more common (45.1%) than elevated hs-cTnI, without significant differences between the subgroups. Patients with PMI showed higher postoperative hs-cTnI concentrations, with median values of 77.3 ng/L (58.2–175 ng/L) at 24 hours and 77.0 ng/L (38.6–189 ng/L) at 48 hours after surgery, compared with patients without PMI (table 2). The median hs-cTnI was 77.3 ng/L (58.2–175) at 24 hours, remaining similarly elevated at 48 hours. Median NT-proBNP concentrations were also higher in patients with PMI at 24 hours (500 ng/L (265–846)) and at 48 hours (444 ng/L (205–899)) compared with patients without PMI, indicating sustained postoperative cardiac

Table 1 Baseline characteristics of the whole population and PMI/non-PMI subgroups

Variable	All patients n=475	PMI n=56 (11.8%)	Non-PMI n=419 (88.2%)	P value
Demographics				
Age (mean, SD), years	67.6±9.4	68.3±8.3	67.5±9.6	0.56
Height (mean, SD), cm	165.9±8.8	168.1±8	165.7±8.8	0.53
Weight (mean, SD), kg	73±14.7	71.8±13.8	73.2±14.8	0.49
BMI (mean, SD)	26.5±4.6	25.3±3.9	26.6±4.7	**0.02**
Men, n (%)	272 (57.3)	36 (64.3)	236 (56.3)	0.26
Women, n (%)	203 (42.7)	20 (35.7)	183 (43.7)	
RCRI				
I	400 (84.2)	43 (76.8)	357 (85.2)	0.13
II	66 (13.9)	13 (23.2)	53 (12.6)	
III	8 (1.7)	0 (0)	8 (1.9)	
IV	1 (0.2)	0 (0)	1 (0.2)	
Medical history				
Hypertension	255 (53.7)	32 (57.1)	223 (53.2)	0.58
Hyperlipidaemia	247 (52.0)	29 (51.8)	218 (52.0)	0.93
Diabetes mellitus	82 (17.3)	10 (17.9)	72 (17.2)	0.91
COPD	106 (22.3)	12 (21.4)	94 (22.4)	0.85
Chronic anaemia	22 (4.6)	1 (1.8)	55 (13.1)	0.49
Atrial fibrillation	41 (8.6)	3 (5.4)	52 (12.4)	0.45
History of cardiac arrest	3 (0.6)	0 (0)	3 (0.7)	1.0
Coronary heart disease	31 (6.5)	1 (1.8)	55 (13.1)	0.15
Cardiac revascularisation	17 (3.6)	0 (0)	17 (4.1)	0.25
Cardiac revascularisation 6 months before	1 (0.2)	0 (0)	1 (0.2)	1.0
Congestive heart failure	10 (2.1)	0 (0)	10 (2.3)	0.61
Stroke	19 (4.0)	7 (12.5)	12 (2.9)	**0.004**
TIA	3 (0.6)	1 (1.8)	2 (0.5)	0.31
Peripheral arteriopathy	24 (5.1)	3 (5.4)	21 (5.0)	0.75
Pulmonary embolism	11 (2.3)	1 (1.8)	10 (2.4)	1.0
Deep vein thrombosis	17 (3.6)	0 (0)	17 (4.1)	0.24
Smoking history	316 (66.5)	48 (85.7)	268 (64.0)	**0.001**
History of COVID	62 (13.1)	7 (12.5)	55 (13.1)	0.89
History of neoplasia	281 (59.2)	29 (51.8)	252 (60.1)	0.23
Laboratory values				
Preoperative haemoglobin (g/L) (mean, SD)	136.7±16.4	138.9±14.7	136.4±16.6	0.28
<90	3 (0.7)	0 (0)	3 (0.7)	0.23
91–119	77 (16.2)	5 (8.9)	72 (17.2)	
>120	395 (83.2)	51 (91.1)	344 (82.1)	

Continued

Table 1 Continued

Variable	All patients n=475	PMI n=56 (11.8%)	Non-PMI n=419 (88.2%)	P value
Preoperative creatinine (µmol/L) (median, IQR)	74.3 (62.9–89.3)	71 (61.0–90.2)	74.3 (62.9–89.1)	0.96
eGFR (mL/min/1.73 m^2)				
<30	7 (1.5)	4 (7.1)	3 (0.7)	**0.001**
30–44	19 (4.0)	2 (3.6)	17 (4.0)	
45–59	43 (9.1)	2 (3.6)	41 (9.8)	
≥60	405 (85.3)	48 (85.7)	357 (85.2)	
Preoperative ECG				
Sinus rhythm	411 (92.2)	51 (91.1)	360 (85.9)	0.93
Atrial fibrillation	9 (2.0)	1 (1.8)	8 (1.9)	
Flutter	3 (0.7)	0 (0)	3 (0.7)	
Other rhythms	23 (5.2)	3 (5.4)	20 (4.8)	

Values in bold indicate statistical significance (p<0.05).
BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (using the CKD-EPI formula); PMI, perioperative myocardial injury; RCRI, Revised Cardiac Risk Index; TIA, transient ischaemic attack.

Table 2 Preoperative and postoperative concentrations of cardiac biomarkers

	All patients n=475	PMI n=56	Non-PMI n=419	P value
Preoperative				
hs-cTnI*	3.3 (3.0–6.0)†	4.7 (3.0–7.0)	3.1 (2.9–5.8)	**0.005**
hs-cTnI ≥45 (n (%))	4 (0.9)	1 (1.8)	3 (0.8)	0.41
NT-proBNP*	110 (59–228)†	132 (73–281)	108 (56–222)	**0.057**
NT-proBNP ≥125 (n (%))	214 (45.1)	29 (51.8)	185 (44.2)	0.31
Postoperative				
24 hours				
hs-cTnI	8.5 (4.7–17.7)	77.3 (58.2–175)	7.8 (4.1–12.9)	**<0.001**
hs-cTnI ≥45 (n (%))	48 (10.1)	45 (80.6)	3 (0.7)	**<0.001**
NT-proBNP	306 (176–547)	500 (265–846)	289 (168–534)	**0.001**
NT-proBNP ≥300 (n (%))	218 (45.9)	35 (62.5)	183 (43.7)	**0.005**
48 hours				
hs-cTnI	8.7 (4.7–17)	77.0 (38.6–189)	7.2 (4–13.3)	**<0.001**
hs-cTnI ≥45 (n (%))	39 (8.2)	36 (64.3)	3 (0.7)	**<0.001**
NT-proBNP	263 (146–551)	444 (205–899)	244 (142–517)	**0.001**
NT-proBNP ≥300 (n (%))	174 (36.6)	33 (58.9)	141 (33.6)	**0.001**

Values in bold indicate statistical significance (p<0.05).
*Both hs-cTnI and NT-proBNP are expressed as median (range).
†Both hs-cTnI and NT-proBNP concentrations are expressed in nanograms per litre (ng/L).
hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; PMI, perioperative myocardial injury.

stress (p=0.001 for both). NT-proBNP concentrations ≥300 ng/L occurred in 45.9% and 36.6% of the cohort at 24 and 48 hours, respectively, with a higher proportion in the PMI group (62.5% vs 43.7%, p=0.005 at 24 hours; 58.9% vs 33.6%, p=0.001 at 48 hours).

Regarding surgical and intraoperative variables (online supplemental table 2), median surgery duration was significantly longer in the PMI group (3.5 hours (2.8–4.4)) compared with the non-PMI group (2.7 hours (1.7–3.8); p<0.001). The frequency of open surgery did not differ between groups (17.9% in patients with PMI vs 9.3% in patients without PMI; p=0.07).

A significant difference existed in the types of pulmonary resections performed: pneumonectomy was exclusive to the PMI group (7.1%), while lobectomy or bilobectomy was more common in patients with PMI (64.3% vs 50.4%; p<0.001). Intraoperative hypotension (ie, systolic blood pressure (SBP) >20% and episodes of SBP <90 mm Hg) was similar between groups; but bleeding was more frequent (12.5% vs 6.2%) in patients with PMI, though not significantly (p=0.093). ECG changes from baseline were infrequent (2.3% overall), with no group differences in new admissions or reinterventions.

Multivariate logistic regression (table 3) included patients (n=454) with at least one postoperative determination of both biomarkers. Severe renal dysfunction (eGFR <30 mL/min/1.73 m^2) and history of smoking were strongly associated with PMI (renal dysfunction: OR 12.25, 95% CI 2.41 to 62.29, p=0.003; smoking: OR 2.78, 95% CI 1.24 to 6.23, p=0.013). Video-assisted thoracic surgery (VATS) was used as the reference surgical technique; by comparison, robotic-assisted thoracic surgery was associated with a higher PMI risk (OR 2.29, 95% CI 1.14 to 4.58; p=0.019), while open surgery showed no significant association (OR 1.61, 95% CI 0.66 to 3.89; p=0.29). Anatomical pulmonary resections (OR 2.01, 95% CI 1.05 to 3.83; p=0.034), postoperative ECG changes from baseline (OR 4.04, 95% CI 1.01 to 16.23; p=0.048) and prior stroke (OR 3.28, 95% CI 1.15 to 9.36; p=0.026) were also linked with higher PMI risk. To partially address potential confounding by demographic or renal factors, an exploratory multivariable logistic regression including hs-cTnI and NT-proBNP, adjusted for age, sex and their interaction, was conducted. No clear variation in biomarker associations with PMI was observed across age or sex (data not shown), and these analyses should be interpreted cautiously given the limited sample size. Regarding renal function, only seven patients had eGFR <30 mL/min/1.73 m^2, which precluded robust interaction or stratified analyses in this subgroup.

At the 30-day follow-up (table 4), MACE occurred in 4.6% of patients (n=22) and was more common in patients with PMI (14.3% vs 3.3%; p<0.001). MI occurred in 0.4% of the cohort, with a higher but not statistically significant incidence in patients with PMI (1.8% vs 0.2%;

Table 3 Multivariate logistic regression analysis of factors associated with PMI

		SE	OR	95% CI	P value
eGFR <30 mL/min/1.73 m^2		0.83	12.25	2.41 to 62.29	**0.003**
History of smoking		0.41	2.78	1.24 to 6.23	**0.013**
Surgical approach	VATS (reference)				0.057
	RATS	0.35	2.29	1.14 to 4.58	**0.019**
	Open surgery	0.45	1.61	0.66 to 3.89	0.29
Stroke		0.53	3.28	1.15 to 9.36	**0.026**
ECG changes		0.71	4.04	1.01 to 16.23	**0.048**
Type of pulmonary resection	Lobectomy/pneumonectomy	0.33	2.01	1.05 to 3.83	**0.034**
Constant		0.44	0.026		**<0.001**

Values in bold indicate statistical significance (p<0.05).
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate (using the CKD-EPI formula); PMI, perioperative myocardial injury; RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracic surgery.

p=0.093). No cardiac arrest cases were reported. Heart failure, stroke and transient cerebrovascular accidents were rare, occurring in 0.2% of patients, all within the non-PMI group (p=0.71). New-onset atrial fibrillation (7.1% vs 1.7%; p=0.011) and other arrhythmias (5.3% vs 0.2%; p<0.001) were more frequent in patients with PMI. Pulmonary thromboembolism was rare (0.4%) and only observed in patients without PMI (p=0.60). Mortality was 1.1% overall, with higher incidence in patients with PMI (3.6% vs 0.7%; p=0.049).

MACE occurrence varied according to the combination of biomarkers (table 5 and figure 2). Patients who were negative for both biomarkers (hs-cTnI−/NT-proBNP−) comprised 40.5% of all measurements and exhibited the lowest 30-day MACE rate (2.7%; reference group). Among patients with hs-cTnI−/NT-proBNP+ (46.5%), the MACE risk increased to 4.3% (OR 1.60, 95% CI 0.53 to 4.85; p=0.410). Patients with only hs-cTnI positivity (hs-cTnI+/NT-proBNP−) comprised 2.9% and had a MACE rate of 7.7% (OR 2.98, 95% CI 0.32 to 27.61; p=0.336). In contrast, the highest risk was observed in patients with dual biomarker positivity (hs-cTnI+/NT-proBNP+) comprising 10.1% and with a 15.2% MACE rate (OR 6.43, 95% CI 1.94 to 21.31; p=0.002). At any level of hs-cTnI status, postoperative NT-proBNP elevation was associated with an incremental increase in 30-day MACE risk, highlighting the complementary prognostic value of combining myocardial injury and haemodynamic stress biomarkers.

Table 4 MACE incidence at 30-day follow-up

Complications during hospitalisation and 30-day follow-up	All patients n=475 (%)	PMI n=56 (%)	Non-PMI n=419 (%)	P value*
MACE	22 (4.6)	8 (14.3)	14 (3.3)	**<0.001**
Non-fatal cardiac arrest	0	0	0	
Myocardial infarction	2 (0.4)	1 (1.78)	1 (0.2)	0.093
Congestive heart failure	1 (0.2)	0 (0)	1 (0.2)	0.71
Stroke	1 (0.2)	0 (0)	1 (100)	0.71
Transient cerebrovascular accident	1 (0.2)	0 (0)	1 (0)	0.71
New-onset atrial fibrillation	11 (2.3)	4 (7.1)	7 (1.7)	**0.011**
New-onset arrhythmia	4 (0.8)	3 (5.3)	1 (0.2)	**<0.001**
Pulmonary thromboembolism	2 (0.4)	0 (0)	2 (0.5)	0.60
All-cause death	5 (1.1)	2 (3.6)	3 (0.7)	**0.049**

Values in bold indicate statistical significance (p<0.05).
*Statistical significance between the PMI and non-PMI groups.
MACE, major adverse cardiovascular events; PMI, perioperative myocardial injury.

Given the higher incidence of MACE in patients with combined postoperative elevation of hs-cTnI and NT-proBNP, we evaluated the characteristics of this subgroup (table 6). A total of 49 patients met the dual biomarker criteria at either 24 or 48 hours after surgery. Compared with patients with any or only isolated biomarker elevation, this subgroup did not differ substantially in major cardiovascular risk factors such as hypertension, diabetes, dyslipidaemia, chronic obstructive pulmonary disease or prior revascularisation, although they more frequently had preoperative stroke (p=0.001), active smoking (p=0.001) and severely reduced renal function (eGFR <30 mL/min/1.73 m^2; p=0.008). These patients underwent longer surgical procedures, predominantly endoscopic lobectomies (median duration 3 hours 42 min, range 1–7 hours 42 min), consistent with greater perioperative stress. Nevertheless, only seven of the observed MACE (14.3%) occurred in the group, primarily cardiac rhythm alterations, with only one acute MI. Despite a higher prevalence of some risk factors in this subgroup, about one-third (31.8%) of MACE in the overall cohort occurred in patients without dual biomarker elevation, indicating that baseline clinical characteristics alone are not enough to predict postoperative events.

To find the main determinants of MACE, we also analysed the profile of the 22 patients with these events. Although the number of MACE events was limited,

Table 5 Association between postoperative biomarkers' positivity and 30-day MACE occurrence

Biomarker combination		Total measurements* n (%)	MACE n (%)	No MACE n (%)	OR (95% CI)	P value versus reference
hs-cTnI–	NT-proBNP–	184 (40.5)	5 (2.7)	179 (97.3)	Reference	
hs-cTnI+	NT-proBNP–	13 (2.9)	1 (7.7)	12 (92.3)	2.98 (0.32 to 27.61)	336
hs-cTnI–	NT-proBNP+	211 (46.5)	9 (4.3)	202 (95.7)	1.60 (0.53 to 4.85)	410
hs-cTnI+	NT-proBNP+	46 (10.1)	7 (15.2)	39 (84.8)	6.43 (1.94 to 21.31)	002

*Number of measurements obtained in the patients with at least one postoperative value of both biomarkers.
hs-cTnI, high-sensitivity cardiac troponin I; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-brain natriuretic peptide.

preventing formal statistical comparisons, cardiovascular risk factors were highly prevalent in the overall cohort and in the subgroup in which MACE events occurred. We found antecedents of hypertension and smoking in 77% of cases and of stroke and coronary artery disease in 9.1%; remarkably, eGFR ≥60 mL/min/1.73 m^2 was observed in 77% of patients. Median surgical duration was 3 hours 59 min (range: 30 min to 7 hours 39 min); surgery procedures were mostly endoscopic (72.7%) and mainly lobectomies (77%). PMI was present in 36.4% of patients. Thus, MACE patients presented a pattern not different from that observed in patients with dual biomarker positivity. However, the distribution of events varied markedly according to the biomarker combinations presented. 15 events occurred in NT-proBNP+ patients, while only eight in those with hs-cTnI+; deaths (n=5), not considered among MACE, were only registered in NT-proBNP+ groups as well as most cardiac rhythm alterations (n=9). These findings suggest that NT-proBNP adds incremental prognostic value beyond hs-cTnI and baseline clinical risk factors.

DISCUSSION

Our study demonstrates that NT-proBNP significantly enhances the prognostic performance of hs-cTnI for predicting major cardiovascular events in patients undergoing thoracic surgery. The combined use of both biomarkers allows a more accurate identification of high-risk patients and may support improved perioperative risk stratification and clinical decision-making.[19 25–27]

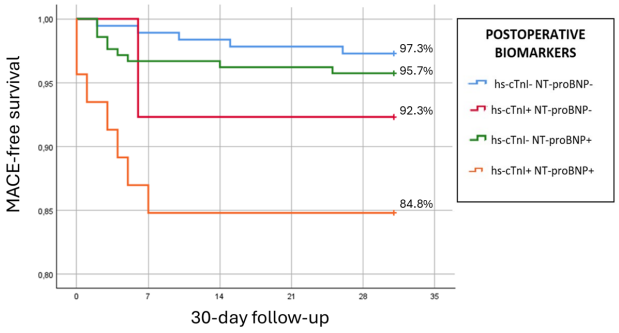

Figure 2 Kaplan-Meier curves of 30-day MACE-free survival stratified by postoperative biomarker status. hs-cTnI, high-sensitivity cardiac troponin I; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 6 Characteristics of the patient subgroup with elevated hs-cTnI and elevated NT-proBNP after surgery

n=49		
Medical history		
Hypertension (%)		40 (81.6)
Hyperlipidaemia (%)		25 (51)
Diabetes mellitus (%)		7 (14.3)
Smoking history (%)		42 (85.7)
eGFR (%)	<30 mL/min/1.73 m^2	4 (8.1)
	30–59 mL/min/1.73 m^2	4 (8.1)
	≥60 mL/min/1.73 m^2	41 (83.7)
History of cardiac arrest		0
Coronary heart disease (%)		2 (4.1)
Cardiac revascularisation (%)		1 (2)
Stroke (%)		7 (14.3)
Transient ischaemic attack (%)		1 (2)
Peripheral arteriopathy (%)		3 (6.1)
Congestive heart failure		0
Pulmonary embolism (%)		1 (2)
Deep vein thrombosis		0
Atrial fibrillation (%)		3 (6.1)
Surgery type and duration		
Open (%)		7 (14.3)
RATS (%)		12 (24.5)
VATS (%)		30 (61.22)
Length, median (range)		3 hours 42 min (1–7 hours 42 min)
MACE		
Total MACE (%)		9 (18.4)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate (using the CKD-EPI formula); hs-cTnI, high-sensitivity cardiac troponin I; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-brain natriuretic peptide; RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracic surgery.

The incidence of PMI in our cohort (11.8%) was slightly lower than that reported in previous large studies.[2 21 29] This difference is likely attributable to several factors. First, the majority of patients (89.7%) underwent minimally invasive procedures, predominantly VATS, which is associated with lower surgical stress and fewer cardiovascular complications than open approaches.[31 32] Second, we used hs-cTnI rather than hs-cTnT, which may result in different diagnostic rates across studies. Prior cohorts, such as VISION and Basel Perioperative Myocardial Injury (BASEL-PMI), mainly relied on hs-cTnT assays,[1 2 10] whereas in the BASEL-PMI study, PMI was detected in 6.1% of patients using hs-cTnI and in 11.3% using hs-cTnT with similar diagnostic criteria.[10] Finally, our definition of PMI required both preoperative and postoperative measurements, thereby reducing the risk of misclassifying chronically elevated troponin concentrations as acute myocardial injury.[33]

Several clinical and procedural factors were independently associated with PMI. Preoperative renal dysfunction (eGFR <30 mL/min/1.73 m^2), smoking history, lower BMI values and prior stroke were among the strongest clinical predictors, while longer surgical duration and pneumonectomy were the most relevant intraoperative variables. These findings are consistent with previous studies identifying renal insufficiency, smoking and surgical complexity as important contributors to PMI.[5 6 34 35] In contrast, RCRI showed limited predictive value in our cohort, suggesting that traditional cardiac risk scores may not fully capture the specific risk profile of patients undergoing thoracic surgery and highlighting the need for procedure-specific risk stratification models.[36 37]

PMI was strongly associated with adverse clinical outcomes. Patients with PMI experienced significantly higher rates of MACE and increased 30-day mortality compared with patients without PMI.[1 9 16] Notably, the highest risk subgroup consisted of patients with postoperative elevation of both hs-cTnI and NT-proBNP, among whom the incidence of MACE reached 15.2%. Among patients with PMI, the presence of elevated NT-proBNP approximately doubled the risk of MACE compared with those with isolated hs-cTnI elevation. Arrhythmias, particularly atrial fibrillation, were the most frequent cardiovascular events, underscoring the clinical relevance of combined biomarker assessment for identifying patients who may benefit from closer monitoring and targeted perioperative management.[22–24 38 39]

Our findings support the growing evidence that perioperative cardiac biomarkers play a central role in the detection of myocardial injury and guiding risk stratification after non-cardiac surgery.[2 7 40] Current guidelines[7 8] already recommend perioperative troponin monitoring in high-risk patients, although standardised therapeutic strategies for PMI remain poorly defined. Previous studies have shown that cardiology consultation and early pharmacological management may reduce mortality in patients with myocardial injury after surgery.[15 41] In our cohort, all patients with PMI received cardiology assessment, and management was individualised according to clinical presentation. Although our study was not designed to evaluate treatment strategies, the observed excess mortality in patients with PMI reinforces the need for multidisciplinary approaches and suggests that incorporating NT-proBNP alongside troponin measurements may further refine clinical risk assessment and follow-up strategies.

Limitations and strengths

The study has several limitations. First, the relatively small sample size may limit the statistical power, particularly for the predictive value of biomarkers. Additionally, owing to the absence of postoperative complications, many patients were discharged early, which precluded 48-hour biomarker assessments and may have affected the completeness of postoperative monitoring. Second, the 30-day follow-up period may have missed cardiovascular complications that manifest beyond the study window. Third, the lack of a standardised PMI definition complicates direct comparisons with other studies. Fourth, using fixed hs-cTnI and NT-proBNP thresholds without adjusting for age and sex may reduce risk stratification accuracy and require tailored adjustments for diverse patient populations. In particular, the NT-proBNP threshold may not fully reflect a cohort with multiple conditions that can independently alter natriuretic peptide concentrations. Additionally, reliance on a specific immunoassay for hs-cTnI may limit external validity of findings. Finally, excluding urgent or emergency surgeries, and patients with severe heart failure, may limit generalisability to higher risk populations.

Our study has several important strengths. First, it provides integrated preoperative and postoperative hs-cTnI and NT-proBNP measurements, in line with recent international guidelines; remarkably, our design predated these recommendations but aligns with them. This dual marker approach offers a more accurate model for predicting MACE compared with troponin alone. Second, employing a hs-cTn assay enhances the precision of PMI detection and refines risk stratification. Third, the specific focus on thoracic surgery patients provides relevant insights into this under-represented population. Fourth, the multicentre design involving three Spanish university hospitals strengthens the external validity of the findings. Fifth, identification of modifiable risk factors, such as smoking and renal dysfunction, underscores opportunities for targeted preoperative management. Finally, serial cardiac biomarker measurements provide an objective, readily available, inexpensive and relatively cost-effective approach that requires fewer resources and less clinical effort while maintaining diagnostic value.

In conclusion, systematic perioperative assessment of hs-cTnI and NT-proBNP improves the identification of patients at increased cardiovascular risk. This dual biomarker approach provides incremental prognostic information and may support more refined perioperative

risk stratification. The potential impact of this strategy on patient outcomes requires further investigation.

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Contributors MA, EP and MdN were involved in the design, conceptualisation and methodology of the study. MA wrote the first draft of the manuscript. MdN, EP and JOL contributed to formal analysis, data interpretation, visualisation, supervision and writing—review and editing. MdM, ÁGO and AGT contributed to methodology, project administration and writing—review and editing. AJ, JT, EMT, AMG, AP, GP, LT and DB were involved in project administration, data curation, review and editing. JSR contributed to formal analysis, data interpretation, review and editing. All authors provided critical revisions and approved the final version of the manuscript. MdN obtained funding for this work. MdN is responsible for the overall content as guarantor.

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Ethics approval This study involves human participants and was approved by the Ethics Research Committees of the three participating university hospitals: Hospital Vall d'Hebron, Barcelona, Spain (15 January 2021); Hospital Santa Creu i Sant Pau, Barcelona, Spain (14 April 2021); and Hospital Ramón y Cajal, Madrid, Spain (14 June 2021) (Protocol ID: PR(AG)621/2020). The study was conducted in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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