



BMJ Open Study protocol for an observational cohort evaluating incidence and clinical relevance of perioperative elevation of high-sensitivity troponin I and N-terminal pro-brain natriuretic peptide in patients undergoing lung resection

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ABSTRACT

Introduction Myocardial injury after non-cardiac surgery has been defined as myocardial injury due to ischaemia, with or without additional symptoms or ECG changes occurring during or within 30 days after non-cardiac surgery and mainly diagnosed based on elevated postoperative cardiac troponin (cTn) values. In patients undergoing thoracic surgery for lung resection, only postoperative cTn elevations are seemingly not enough as an independent predictor of cardiovascular complications. After lung resection, troponin elevations may be regulated by mechanisms other than myocardial ischaemia. The combination of perioperative natriuretic peptide measurement together with high-sensitivity cTns may help to identify changes in ventricular function during thoracic surgery. Integrating both cardiac biomarkers may improve the predictive value for cardiovascular complications after lung resection. We designed our cohort study to evaluate perioperative elevation of both high-sensitivity troponin I (hs-TnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients undergoing lung resection and to establish a risk score for major cardiovascular postoperative complications.

Methods and analysis We will conduct a prospective, multicentre, observational cohort study, including 345 patients undergoing elective thoracic surgery for lung resection. Cardiac biomarkers such as hs-TnI and NT-proBNP will be measured preoperatively and at postoperatively on days 1 and 2. We will calculate a risk score for major cardiovascular postoperative complications based on both biomarkers' perioperative changes. All patients will be followed up for 30 days after surgery.

Ethics and dissemination All participating centres were approved by the Ethics Research Committee. Written informed consent is required for all patients before inclusion. Results will be disseminated through publication in peer-reviewed journals and presentations at national or international conference meetings.

Trial registration number NCT04749212.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first study to integrate serial measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hs-TnI) biomarkers, more sensitive and specific for early detection of cardiovascular complications after lung resection.
- ⇒ The hs-TnI assay used in our study is more sensitive and accurate to detect low concentrations, contributing to a probable increase in detection of myocardial injury after non-cardiac surgery (MINS) than detected with conventional cardiac troponin assays.
- ⇒ Determining the clinical significance of hs-TnI elevation (due to ischaemic or non-ischaemic causes) may be crucial in the development of diagnostic and therapeutic protocols, aimed at improving MINS prognosis in patients undergoing thoracic surgery for lung resection.
- ⇒ The results of our study may be difficult to compare with previously published works, due to differences in methodology, especially when using both a hs-TnI assay, together with NT-proBNP.
- ⇒ Our protocol is designed as a short-term (30 days follow-up) study, therefore, long-term studies for better understanding of NT-proBNP and hs-TnI efficiency will be still needed.

INTRODUCTION

Myocardial injury is usually presented as acute coronary syndrome, manifested as myocardial infarction (MI) or unstable angina, and associated with symptoms as chest pain or shortness of breath.¹ However, perioperative myocardial injury after non-cardiac surgery (MINS), apparently triggered by myocardial

oxygen supply–demand mismatch and mostly silent, is presented as an isolated cardiac troponin (cTn) elevation without signs or symptoms or ECG changes.² Therefore, MINS term derived from a large observational study and is defined as myocardial injury due to ischaemia occurring during or within 30 days after non-cardiac surgery and mainly diagnosed based on elevated cTn values.³ The incidence of MINS is quite elevated, especially in patients undergoing thoracic surgery, and is usually related to several additional factors: smoking status, type and length of the surgery, pericardial incision or intraoperative use of vasoactive drugs.⁴ Based on available evidence postoperative cTn elevation is an independent predictor of 30-day mortality in high-risk non-cardiac surgery patients.⁵ Without cTn measurements, many ischaemic episodes may go missed and underdiagnosed. Routine perioperative monitoring of cardiac biomarkers is highly recommended⁶ and supported by recent guidelines in patients with high cardiovascular risk.^{5,7}

MINS in thoracic surgery

In patients undergoing thoracic surgery serial cTn monitoring seems reasonable, considering the frequent use of high doses of analgesics in postoperative settings. Serial cTn monitoring, previously indicated only by cardiac symptoms or ECG changes, would help identify subclinical myocardial injuries with prognostic significance in patients susceptible to cardiovascular complications. In patients undergoing thoracotomy and lung surgery, cTn has been proven a reliable biomarker for myocardial injury detection.⁸ Although cTn elevations are mainly associated with intrapericardial resection and pneumonectomy, the available evidence about incidence varies greatly (0%–49%). The routine use of cTn monitoring in patients undergoing thoracic surgery is not yet implemented, and its predictive value is still unclear.^{5,9–15} The table 1 summarises available studies using different cTn assay measurements in thoracic surgery patients.

During the last years, most hospitals have replaced conventional cTn assay with the new generation high-sensitivity cTn assays which are more accurate and sensitive to detect myocardial ischaemia, being more precise at

an earlier time and in lower concentrations,¹⁶ therefore considered more precise prognostic tools. There is only one available study, published by our group, which used a high-sensitivity troponin I (hs-TnI) assay (ADVIA Centaur Siemens analyser) in high-risk thoracic surgery patients, where the overall incidence of MINS (defined as at least one elevated value of hs-TnI ≥ 0.04 ng/mL at the first two postoperative days) was 27%.⁴ In this study, no significant association between MINS and 30-day mortality was observed. Therefore, the elevated incidence of MINS after thoracic surgery, the independent relationship with the extent of lung resection, as well as the fact that MINS was not associated with greater short-term mortality, may suggest nonischaemic causes for the hs-TnI elevation in thoracic surgery patients.

Natriuretic peptides as cardiac biomarkers

Natriuretic peptides are vasodilator hormones responsible for regulation of blood pressure and volume homeostasis. B-type natriuretic peptide (BNP) and its inactive cleavage product, N-terminal fragment (NT-proBNP), are produced and secreted by ventricular myocytes in response to ventricular wall stretching, myocardial ischaemia and endocrine modulation through other neurohormones such as norepinephrine, glucocorticoids or proinflammatory cytokines.^{17,18} Both NT-proBNP and BNP are useful for detection in plasma, but NT-proBNP has a longer plasma half-life and therefore persists at a higher concentration when compared with BNP. NT-proBNP is accepted to be biochemically more stable than BNP,¹⁹ thereby fewer requirements are needed to protect its degradation. Moreover, scaling varies among BNP assays while NT-proBNP assays are already standardised, and there is no simple conversion factor to compare BNP and NT proBNP levels.²⁰

Natriuretic peptides are commonly used for the diagnosis and management of congestive heart failure.²¹ However, studies in several types of acute coronary syndromes such as ST-segment myocardial infarction, non-ST elevation myocardial infarction or unstable angina, have shown that elevated levels of natriuretic peptides are independently associated with adverse

Table 1 Summary of studies including thoracic surgery patients with cardiac troponin measurements: cut-off values and incidence of troponin elevations

Study/authors	Patients (n)	Cardiac troponin (cTn) assay	Cut-off value	Incidence of cTn elevation
Vikenes <i>et al</i> ⁹	24	cTn I, cTn T	>0.2 ug/L	0%
Lim <i>et al</i> ¹⁰	41	cTn I	>0.04 ug/L	7%
Lucreziotti <i>et al</i> ¹¹	50	cTn I	>0.06 ug/L	20%
Muley <i>et al</i> ¹²	64	cTn I	>0.32 ng/mL	14%
VISION group (2012) ⁵	376	cTn T	>0.03 ng/mL	8.7%
Hua <i>et al</i> ¹³	491	cTn I	>0.04 ng/mL	16%
Puelacher <i>et al</i> ¹⁴	219	hs*-Tn T	≥ 0.14 ng/mL increase from preoperative value	24%
Uchoa and Caramelli ¹⁵	151	cTn I	≥ 0.16 ng/mL	49%
González-Tallada <i>et al</i> ⁴	177	hs*-Tn I	≥ 0.04 ng/mL	27%

*High-sensitivity cardiac troponin.

outcomes, especially mortality²² and could be used as prognostic markers.

Natriuretic peptides in the perioperative setting

Nowadays, there is growing evidence that BNP measurement is an independent predictor of perioperative and long-term complications related to non-cardiac surgical procedures and is also independently associated with the composite outcome of death and non-fatal MI at 30 and 180 postoperative days.²³ Recent meta-analysis of 18 studies including at least 2000 patients examined the role of postoperative natriuretic peptides as predictors of postoperative complications. Patients with postoperative BNP ≥ 245 pg/mL or NT-proBNP ≥ 718 pg/mL had significantly greater risk for 30-day mortality or non-fatal MI (OR 4.5, 95% CI 2.75 to 7.4), mortality (OR 4.5, 95% CI 2.29 to 7.69) and cardiac failure (OR 18.5, 95% CI 4.55 to 75.29).²⁰

The results of nested VISION substudy in 10 402 patients undergoing non-cardiac surgery, showed a strong association between NT-proBNP elevation, vascular death and MINS within 30 days. Results of this cohort showed that patients with NT-proBNP values < 200 pg/mL presented a risk of death or MI of $\leq 3\%$, compared with patients with NT-proBNP values between 200 and < 1500 pg/mL, where risk of death or MI was 7.9%.²⁴ Furthermore, authors concluded that NT-proBNP may be a helpful tool in identifying patients at higher risk of postoperative cardiac events and who may benefit from perioperative troponin monitoring.

Natriuretic peptides in thoracic surgery

Both BNP and NT-proBNP have been reported to reflect postoperative right ventricular dysfunction,²⁵ and to be an effective predictor of atrial fibrillation,^{26–30} as well as a high-quality predictor of postoperative cardiopulmonary complications in elderly patients with lung resection by cancer.^{18 31} Furthermore, some studies tried to establish thresholds of NT-proBNP (> 30 pg/mL) for postoperative complications in elderly patients.^{31 32} A meta-analysis of five studies including 742 elective thoracic surgery patients, showed that elevated preoperative NT-proBNP levels were associated with an OR 3.13 (95% CI 1.38 to 7.12; $I^2=87\%$) for postoperative atrial fibrillation.³⁰ Based on this evidence, a recent study conducted by Amar *et al* including 635 patients developed a brain peptide prediction model for atrial fibrillation after thoracic surgery.³³ Another recent study conducted by Cagini *et al* with 294 patients undergoing elective pulmonary resection, showed BNP levels measured at 24 hours after surgery to be an independent predictor of postoperative complications, with an association between BNP elevation and an increased risk for adverse cardiopulmonary events.¹⁸ In conclusion, it seems plausible that perioperative natriuretic peptide measurement may help identify changes in ventricular function during thoracic surgery.

We designed our cohort study to evaluate the incidence and magnitude of perioperative NT-proBNP and

hs-TnI elevations in patients undergoing lung resection. Our study will also evaluate: (1) NT-proBNP and/or hs-TnI elevation's association with major cardiovascular complications (non-fatal cardiac arrest, acute myocardial infarction, angina, congestive heart failure, new clinically significant atrial fibrillation, cardiovascular death); (2) perioperative variables associated with NT-proBNP and hs-cTnT elevations; and (3) predictive value of NT-proBNP and hs-TnI for cardiovascular complications.

METHODS AND ANALYSIS

Study design

The current study is a prospective, multicentre, observational cohort including 345 patients undergoing elective thoracic surgery for lung resection. The study will be carried out in three University Spanish hospitals performing the largest number of thoracic surgeries per year. The study protocol adheres to the STROBE Statements checklist (online supplemental file 1), and is approved by the Ethics Research Committees of each participating hospital. Written informed consent will be obtained from all patients before inclusion (online supplemental file 2). The study is registered at ClinicalTrials.gov.

Study population

We will include patients aged ≥ 45 years old, scheduled for elective thoracic surgery for lung resection (pneumonectomy, lobectomy, bilobectomy or segmentectomy) under general anaesthesia. Patients will be excluded if they meet one of the following criteria: (1) undergoing urgent, emergent or non-thoracic surgery; (2) presence of symptoms related with infection or sepsis and (3) documented history of severe heart failure and/or an ejection fraction less than 30%.

Patient recruitment

Research personnel will screen elective thoracic surgery patients daily, to identify eligible candidates. Potentially eligible patients will be approached and invited to participate in the study. Written informed consent form will be obtained before surgery. Patients will be managed following the routine anaesthetic and surgical protocols of each hospital.

Study procedures

Biomarkers' measurements

All the three participating centres will use the same immunoassay system (Atellica IM Siemens) for measuring both cardiac biomarkers (hs-TnI and NT-proBNP) considering institutional thresholds to define the elevations.

Both biomarkers will be measured in each patient at three time points: preoperatively and at day 1 and day 2 after surgery. Both biomarkers will be added to the routine preoperative or postoperative blood tests, avoiding the need for extra blood samples. In patients with postoperative elevated hs-TnI levels and/or presence of ischaemic

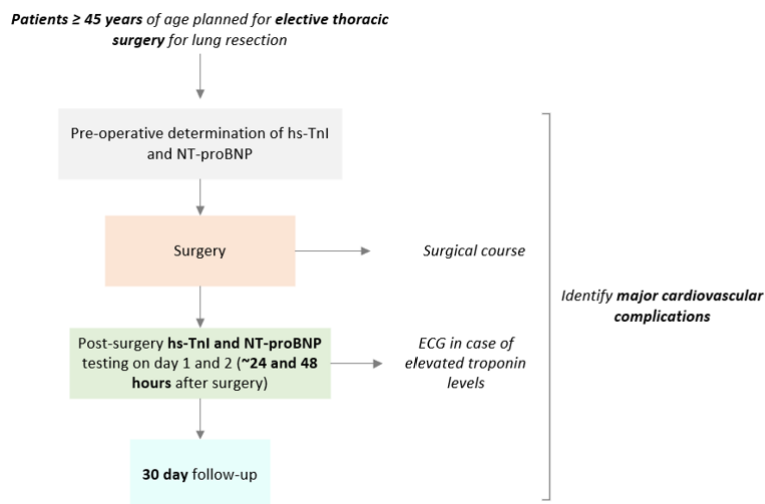


Figure 1 Study organigram. hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide.

symptoms, an ECG will be performed and non-ischaemic causes of hs-TnI elevation will be excluded. All patients will be closely monitored after surgical procedure and for 2 days postoperatively. (figure 1 - Study organigram).

For patients with confirmed MINS, a cardiologist evaluation will be performed. Treatment will be at clinician's discretion considering the patient's cardiovascular risk factors and available guidelines recommendations.⁷

We will try to provide clinical and practical threshold values based on guidelines recommendations, which in turn determine institutional laboratory threshold values. In case of NT-proBNP, two different threshold values will be provided: ≥ 125 pg/mL (for outpatients) used in preoperative setting and ≥ 300 pg/mL (for patients in the emergency department)³⁴ used in postoperative setting. In contrast, only one institutional threshold value for hs-TnI (< 45 ng/L) will be provided, used only in postoperative setting.¹

Follow-up

All recruited patients will be followed up by researchers during hospitalisation until discharge. We will further perform a telephone follow-up on the 30th day after surgery to evaluate major cardiovascular events including non-fatal cardiac arrest, acute myocardial infarction, cardiac revascularisation, congestive heart failure, new clinically significant atrial fibrillation, cardiovascular death and stroke (online supplemental material file 3).

Outcomes

Primary outcome: Perioperative hs-TnI and NT-proBNP elevation in patients scheduled for elective lung resection. Major cardiovascular complications at 30-days: non-fatal cardiac arrest, acute myocardial infarction, cardiac revascularisation, congestive heart failure, new clinically significant atrial fibrillation, cardiovascular death and stroke.

Secondary outcome: MINS.

Variables

1. Preoperative variables: (a) Age; (b) gender; (c) history of ischaemic heart disease: angina, myocardial infarction or acute coronary syndrome, segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect of radionuclide imaging, positive radionuclide exercise, echocardiographic exercise or pharmacological cardiovascular stress test demonstrating cardiac ischaemia and coronary angiographic or computer tomography evidence of atherosclerotic stenosis $\geq 50\%$ of the diameter of any coronary artery; (d) history of cardiac arrest; (e) congestive heart failure; (f) peripheral vascular disease; (g) stroke or transient ischaemic attack; (h) deep venous thrombosis or pulmonary embolism; (i) diabetes mellitus; (j) hypertension; (k) obstructive sleep apnoea; (l) chronic obstructive pulmonary disease; (m) active cancer; (n) history or current smoking; (o) chronic kidney disease; and (p) abnormal ECG prior to surgery (left ventricular hypertrophy, left bundle branch block, ST-T abnormalities).
2. Intraoperative variables: (a) Type of surgical resection: pneumonectomy, bilobectomy, lobectomy, segmentectomy; (b) surgical approach: open, video-assisted thoracic surgery (VATS), VATS-converted to open; (c) side of surgery (right/left); (d) duration of the procedure; (e) type of anaesthesia (volatile or intravenous); (f) use of regional analgesic techniques (thoracic epidural or paravertebral block); (g) intraoperative hypotension (≥ 20 mm Hg decrease from basal mean arterial pressure or a 20% change in mean arterial pressure) and its duration (minutes); and (h) intraoperative blood loss and transfusion requirements (number of Red Blood Cells (RBC)).
3. Postoperative variables: (a) Hypotension (≥ 20 mm Hg decrease from basal mean arterial pressure or a 20% change in mean arterial pressure) and its

duration (minutes) during Post-anaesthesia care unit (PACU)/Intensive care unit (ICU) and stay; (b) major revascularisation, congestive heart failure, new clinically significant atrial fibrillation, cardiovascular death, stroke; (c) pulmonary complications (atelectasis, pulmonary oedema, pneumonia, acute respiratory distress syndrome).

Data collection and data management

We will record data from electronic clinical records of each hospital (baseline, operative assessment and hospital discharge). One month after surgery data will be collected by telephone follow-up. If patients (or relatives) indicate that they have experienced any of the main outcomes, relevant source documents will be obtained.

An electronic case report form (eCRF) will be designed in a secure online database (www.clinapsis.com) to record all the protocol-required information reported for each patient to preserve and maintain quality and integrity of all the data. All clinical records, source documents, follow-up visit logs and CRFs will be locked in the appropriate study files in each site. Only study team members will have access to protected health information. Privacy and confidentiality of the obtained data will be ensured according to Spanish Organic Law 1/1999 of the 3rd of December regarding the protection of personal data. Moreover, a specific database will be generated, with a special identification number as a unique identifier for each patient, to preserve the confidentiality. All completed data will be uploaded and stored in the electronic database previously mentioned with password protected access.

Statistical considerations

Sample size

The primary aim of the study is the incidence of perioperative hs-TnI and NT-proBNP elevation in patients scheduled for elective lung resection. The threshold to define perioperative elevation of hs-TnI is ≥ 45 ng/L (higher than upper reference percentile (upper reference limit (URL))), whereas the threshold to define perioperative elevation of NT-proBNP is ≥ 125 pg/m (higher than institutional value for outpatients). We calculate the sample size according to the results of the previous studies in patients undergoing lung resection, considering an incidence for hs-TnI elevation of 28%⁴ and an incidence of 22% for NT-proBNP elevation,²⁷ assuming a similar incidence in our study. The sample size calculation is based on a formula that derives directly from the method to calculate the CI for estimating a mean of a quantitative variable assuming normal distribution. Sample size and precision estimates for primary endpoints are presented in [table 2](#). We assume that 310 patients will provide a precision (half width of 95% CI) estimate of 23% to 33% for hs-TnI elevation and 17.4% to 26.6% for NT-proBNP elevation at a 95% confidence level. Assuming a drop-out rate of 10%, a total sample size of 345 subjects is planned.

Table 2 Sample size calculation

Sample size and precision estimates for primary endpoints based on previous studies				
	Incidence	Sample size	Precision	95% CI
hs-TnI	28%	310	5%	23% to 33%
NT-proBNP	22%	264	5%	17% to 27%
NT-proBNP	22%	310	4.61%	17.4% to 26.6%

hs-TnI, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Statistical analysis

All variables will be reviewed to prevent inconsistencies, and a flow chart will be designed to describe withdraws from the study. Continuous variables will be presented as the mean and SD or the median and IQR and categorical variables as the count and percentage (%). The univariate relationship between each factor and the cardiovascular complications will be analysed using an independent samples t-test or the Mann-Whitney U test, as appropriate, for the continuous variables and the χ^2 test or Fisher's exact test for dichotomous categorical variables. The OR and the 95% CI for all exposure factors will also be calculated. Multivariable logistic regression analyses will be performed to identify the independent risk factors of major cardiovascular complications and the predictive performance of identified variables will be evaluated using receiver-operating characteristic curve analysis. In order to calculate the adjusted OR as a measure of association between hs-TnI and NT-proBNP elevation and cardiovascular postoperative complications, a score table will be created depending on both biomarkers' perioperative changes. The [table 3](#) defines the independent or predictive variable comparisons of baseline characteristics among the groups categorised by the cut-off values. Comparisons of baseline characteristics among the groups (categorised by the cut-off values) will be assessed by one-way analysis of variance or the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. P values less than 0.05 will be considered significant.

Prognostic thresholds for the prediction of major cardiovascular complications should be associated with a high enough OR result in a post-test probability sufficient to change the perception of clinical risk. We will perform regression analysis using the post-hoc biomarkers thresholds and convert continuous measurement into a dichotomous variable to calculate unadjusted OR for the prediction on postoperative complications.

Study organisation

The study will be coordinated by principal investigator and each hospital will have one lead investigator. Research personnel of all participating hospitals will be responsible for the organisation of the study in the local settings, completing the study database and ensuring high data quality. The research group of the study is made up of multidisciplinary clinical investigators from

**Table 3** Independent or predictive variable comparisons of baseline characteristics among the groups categorised by the cut-off values

Biomarker analysis	Cut-off value	Score
Preoperative NT-proBNP	≥125 pg/mL	1
Postoperative NT-proBNP	≥300 pg/mL	1
Postoperative hs-TnI	≥45 ng/L	1

*Possible score value groups: 0, 1, 2, 3.

hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide.

anaesthesiology, thoracic surgery, clinical epidemiology and biochemistry departments, with large experience in the perioperative setting. The study structure includes Adjudication Committee, Steering Committee, Operations Committee and Monitoring Committee. The Adjudication Committee is composed by clinicians with considerable expertise in perioperative outcomes and will adjudicate all important clinical events. The Steering Committee will supervise the whole project, and the Operations Committee will ensure optimal running of the study. Since our study is designed as an observational cohort a Monitoring Committee will be composed by researchers with substantial experience and knowledge in perioperative medicine and by internal monitoring analysis, which will ensure high data quality, verifying the consistency and accuracy of data entries in the eCRF and other protocol-related documents, as well as verify the adherence to the protocol and the completeness.

Patient and public involvement

No patients were involved in proposing the research question or the outcome measures, nor were they involved in the design or implementation of the study. If patients develop MINS, they will be advised to seek cardiologist consultation. If they are already followed-up by a cardiologist, we will advise to schedule an earlier appointment and to inform doctors about their new condition. There are no plans to disseminate the results of the research to study participants.

Ethics considerations

Ethics approval for this study, with protocol ID: PR(AG)621/2020, was provided by the Ethics Research Committees of three participant hospitals: University Hospital Vall d'Hebron, Barcelona, Spain (M Navarro-Sebastian, MD, 15 January 2021), University Hospital Santa Creu I Sant Pau, Barcelona, Spain (M Alonso-Martinez, MD, 14 April 2021) and University Hospital Ramon y Cajal, Madrid, Spain (M Angeles Gálvez-Múgica, MD, 14 June 2021). The study has been designed according to the Declaration of Helsinki, as a statement of ethical principles for medical research.

Research personnel with good clinical practice will obtain written informed consent for each patient who agrees to participate in the study. Only the researchers

associated with the study and the Ethic Committees will have access to the clinical data. All obtained data will be stored on a secure online database with a special identification number to preserve strict confidentiality.

Dissemination policy

The results obtained from this study will be presented at national or international conferences and will be considered for publication in peer-reviewed scientific journals.

The knowledge dissemination plan includes traditional modes of dissemination (ie, publication in a policy-driving journal, national/international conference presentations), as well as engagement of influential medical organisations. Broader dissemination will be performed by public websites and Twitter accounts of participating hospitals. In addition, dissemination will be conducted in the Spanish Association of Anaesthesiology as well as in the international network of European Society of Anaesthesiology and Intensive Care.

DISCUSSION

Executive summary

In contrast to other non-cardiac surgeries, troponin elevation seems more common after lung resection. Despite the importance of systematic perioperative high-sensitivity cardiac troponin measurements in patients undergoing lung resection, available data is still not compelling which raises major interest. Since troponin elevation after thoracic surgery may be regulated by mechanisms other than myocardial ischaemia (eg, elevation of right ventricular afterload), introduction of systematic perioperative NT-proBNP measurements together with hs-TnI may help identify changes in myocardial function. Therefore, we suggest that integrating both cardiac biomarkers (hs-TnI and NT-proBNP) may better predict postoperative cardiovascular complications in this group of patients. Our data will provide a valuable overview on the pathophysiology of perioperative myocardial injury, crucial for optimising treatment and improving prognosis in patients undergoing lung resection.

Our study in the context of previous research

The present study stands out for being the first up to date in which hs-TnI and NT-proBNP measurements are simultaneously extracted from a considerable sample of patients undergoing thoracic surgery and are directly correlated with cardiovascular complications occurring in the immediate postoperative period.

We believe that the combination of both cardiac biomarkers may improve the predictive value for cardiovascular complications after lung resection as well as potentially improving the management and prognosis of these patients.

Furthermore, determining the diagnostic threshold values of each of these cardiac biomarkers for risk stratification may contribute not only to reducing the morbidity and mortality of patients undergoing non-cardiac surgery

but also in reducing their hospital stay and in consequence the associated costs.

In addition, the multiple variables collected, such as patients' age, previous medical history or medication; as well as the surgical course itself may prove useful in identifying predictive factors for postoperative complications.

Implications for practice and research

The existence of a direct relationship between elevated NT-proBNP and hs-TnI and the appearance of cardiovascular complications could mean that their routine determination in high cardiovascular risk patients should be included in current protocols for the better management of patients undergoing thoracic surgery.

Study's strengths and limitations

Our study has several limitations. First, our protocol is designed as a short-term (30-day follow-up) study, therefore long-term studies for better understanding of efficiency of hs-TnI and NT-proBNP systematic measurements in thoracic surgery patients are still needed. Second, results of our study may be difficult to compare with previously published results, because of differences in methodology when using a hs-TnI assay, together with NT-proBNP. Third, the use of hs-TnI, would only be applicable at centres using the same assay. Fourth, elevation of hs-TnI above the 99th percentile URL has become widely used as an indicator for myocardial injury. Based on guideline recommendations, we have chosen this definition to evaluate the incidence and magnitude of hs-cTnI elevation in patients after lung resection. However, further studies are needed to establish prognostic cut-off values for major cardiovascular complications in these patients.

Our study also has some strengths. First, to our knowledge, this is the first study integrating systematic measurement of hs-TnI and NT-proBNP, preoperatively and postoperatively, which is strongly recommended by recent European Society of Cardiology (ESC)/European Society of Anaesthesiology and Intensive Care (ESAIC) guidelines.⁷ Second, the hs-TnI assay used in our study is more sensitive and accurate in detecting low concentrations, contributing to an over-detection of MINS than would be detected by conventional cTn assays. Third, determining the clinical significance of hs-TnI and NT-proBNP elevations (due to ischaemic or non-ischaemic causes) may be crucial in the development of diagnostic and therapeutic protocols, aimed at improving MINS prognosis in patients undergoing thoracic surgery for lung resection.

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Contributors MdN (principal investigator), MA and EP wrote the first draft of the protocol manuscript. MdN, MA, EP and MdM planned the conceptualisation and the design of the study, and the protocol. AM-G, JP-V, JCT, LG, AG-T, EM-T, EC-G, GP, AdP, DP and AC-T contributed to the design and implementation of the protocol. All authors provided critical revisions to the manuscript before approving the final version. MdN obtained funding for this work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Any data required to support the protocol can be supplied upon reasonable request. The data used in the present study is part of a larger data set. The data not used for this manuscript will be employed in future manuscripts. Technical appendix, statistical code and data set available from the Dryad repository.

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