


BMJ Open Incidence and prognosis associated with troponin elevation after cardiac surgery: a prospective cohort study

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ABSTRACT

Objective Cardiac troponin is used as a prognostic biomarker after cardiac surgery. However, numerous confounding elements, such as inflammation, liver and renal function biomarkers, have been associated with troponin variations. Furthermore, several thresholds regarding the definition of myocardial infarction have been suggested. We aimed to confirm the accuracy of troponin, analysed as time-dependent variable, to predict mortality independently from other biomarkers; and to assess the incidence and prognosis of a 10 times upper normal value threshold (troponin_{10N}) used in the current fourth definition of myocardial infarction.

Methods In a prospective cohort of patients who underwent cardiopulmonary bypass cardiac procedures, we assessed the association between serum levels of troponin, creatinine, bilirubin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), C-reactive protein (CRP), lactate and in-hospital mortality. Several models were tested, including time-dependent Cox regression, survival and latent class analyses. Repetitive measurements were accounted for.

Results We included 3857 patients. In-hospital mortality was 2.8%. Troponin was independently associated with mortality in all models, after adjusting for other biomarkers. Of note, troponin_{10N} was reached in 3830/3857 (99.3%) of patients. Similarly, renal function was independently associated with mortality. Conversely, CRP and liver biomarkers were not associated with mortality, once adjusting for other confounders.

Conclusion We confirmed that troponin increase was independently associated with mortality after cardiac surgery. This association was independent of inflammatory syndrome and renal and liver failure. Troponin_{10N} was reached in almost all patients, questioning the relevance of this criterion to define postoperative myocardial infarctions after cardiac surgery.

INTRODUCTION

Cardiac surgery procedures have a higher risk of postoperative complications, including death, as compared with other surgery procedures. During the postoperative period, forecasting all adverse events to prevent them is a daily challenge for cardiac surgery intensivist physicians.

Among numerous biomarkers, cardiac troponin offers remarkable specificity for

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ In this large single-centre prospective cohort study, all consecutive patients who underwent cardiac surgery with cardiopulmonary bypass were included over a 4-year period.
- ⇒ Biomarkers including troponin levels were routinely assessed during the perioperative period.
- ⇒ The association between in-hospital mortality and biomarkers of interest, including troponin, was assessed using several statistical methods, including survival analysis, mixed-effects models and discrimination evaluation.
- ⇒ Confounding variables such as European System for Cardiac Operative Risk Evaluation II and procedure type were accounted for.

cardiac injury. Its polypeptide structure differs from the sequence of skeletal troponins and rises in myocardial hypoxaemia. It is routinely used for myocardial infarction diagnosis,¹ even after cardiac surgery.² It is also known to yield a prognostic value as an independent factor of mortality in patients without myocardial infarction, in heart failure,³ non-cardiac surgery^{4–6} and even in overall hospitalised population.⁶

After cardiac surgery, troponin has been associated with a reliable prognostic value.^{7,8} Previous studies analysed troponin as a binary single-timepoint variable (ie, elevated or not, at a prespecified time such as day 1 or day 2 after cardiac surgery and with specific threshold values), and the prognostic value of its variation is still unclear. Yet, physicians often reason with relative variations in mind (a percentage variation from baseline value) over various time frames (from a few hours to a few days), which warrants specific statistical analyses.⁹ Moreover, troponin serum levels may be influenced by renal or liver failure and inflammation, elements which alongside impaired cardiac function cannot fully explain the association between troponin elevation and mortality.^{10,11} Finally, numerous troponin elevation thresholds have been

suggested, introducing the concept of myocardial injury after cardiac surgery, which may trigger specific investigations (such as coronary angiography).^{12–14} A threshold of 10 times the upper normal value is common to several, including the fourth universal definition of myocardial infarction.

In the present work, we accounted for repeated troponin level measurements, and performed a longitudinal analysis of this biomarker, to account for temporal variations as well as confounding elements which included renal and liver function and inflammation. Doing so, we aimed to further assess the prognostic value of troponin as a time-dependent variable in a longitudinal cohort of patients who underwent cardiac surgery with cardiopulmonary bypass (CPB). Moreover, we assessed how frequently troponin rose above 10 times its upper normal value and analysed the prognostic value of this threshold.

METHODS

This cohort study included all patients who underwent cardiac surgery in a high-volume cardiac surgery centre (CMC Ambroise Paré, Neuilly-Sur-Seine, France) in a 4-year period between 2015 and 2019. All consecutive patients who underwent cardiac surgery with CPB were included. Exclusion criteria were age inferior to 18 and reintervention in the same hospitalisation.

Data came from the Registry for the Improvement of Postoperative Outcomes in Cardiac and Thoracic Surgery (RIPOSTE) database, registered at ClinicalTrials.gov (NCT03209674). This registry was declared to the Commission Nationale de l'Informatique et des Libertés (CNIL 2109982). The RIPOSTE database recorded prospectively patients' preoperative and postoperative characteristics. Laboratory data were extracted; they included all in-hospital levels of cardiac troponin, creatinine, lactate, transaminases, bilirubin and C-reactive protein (CRP). Follow-up was complete for all patients with a duration equal to that of hospital stay.

Data were collected prospectively for each patient: demographic data, variables required for the computation of European System for Cardiac Operative Risk Evaluation (EuroSCORE II), laboratory data and in-hospital mortality. Echocardiographic parameters were prospectively collected in the database. Data were anonymised per national regulations and used with the approval of an institutional review board committee. Data collection was authorised under French national legislation (CNIL, registration number: 2029657; AMR003). There were no missing data. Throughout the study, all surgery procedures were performed by the same team of surgeons, all of whom performed the same proportion of procedures.

Outcomes and definitions

In-hospital mortality was defined similarly as in the EuroSCORE II study: death occurring in the same hospital where the operation took place before discharge from the hospital. Similarly, all definitions of preoperative

variables are those of EuroSCORE II.¹⁵ Specifically, preoperative critical state referred to ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support or preoperative acute renal failure (anuria or oliguria <10 mL/hour). Redo surgery was defined as a history of cardiac surgery.

Biomarkers

Troponin

Cardiac I-troponin levels were measured with immunoanalysis ABBOTT Architect I2000SR automaton by *chemiluminescent microparticle immunoassay*. Upper normal laboratory value was 0.016 ng/mL in women and 0.034 ng/mL adapted from the 99th percentile of a population of asymptomatic subjects.

Creatininemia

Serum creatinine was assayed using enzymatic method with ABBOTT Architect. Severity degrees of acute kidney injury (AKI) were defined according to Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Stage 1: 1.5-fold to 1.9-fold increase in creatinine or increase of more than 0.3 mg/dL (26.5 µmol/L). Stage 2: 2-fold to 2.9-fold increase from baseline. Stage 3 was defined as an elevation of more than three times compared with baseline or an increase to more than 4 mg/dL (353.6 µmol/L) and acute increase of more than 0.5 mg/dL (44.2 µmol/L).

Statistical analysis

Categorical variables were expressed as absolute number and percentage. Continuous variables were expressed as median and IQR, as Shapiro-Wilk test rejected with a 5% first-order risk normality of the right-skewed data.

Primary analysis was a time-dependent Cox regression model with mixed effects, accounting for repeated measures of troponin, and was designed for survival analysis. A backward stepwise regression starting from all variables with a p value of 0.05 or less was performed to select covariates for the final model in order to optimise both Akaike information criterion (AIC), measuring the relative goodness of fit of the models,¹⁶ and Bayesian information criterion (BIC) which penalises model complexity more heavily,¹⁷ with a theoretical risk of choosing excessively simple models contrary to AIC which tends to select more complex models. We excluded covariates with a high collinearity.

Discrimination performance of troponin, regarding in-hospital mortality, was assessed by building receiver operating characteristic (ROC) curves and by computing the area under the receiver operating characteristic curve with a 95% CI.

Additional analyses focused on peak troponin, instead of time-dependent troponin, using Cox regression models. Finally, we performed a latent class analysis (LCA) with an estimation of joint latent class mixed models. The day

of troponin measure was used in both fixed and random effects. Class membership multinomial logistic model included all variables from the survival analysis. We used a proportional Weibull baseline risk function in each latent class. The optimal number of classes was determined by both optimisation of log-likelihood and BIC.

As secondary analyses, we focused on serum creatinine (as a continuous variable), observed in a time-dependent manner (as described above for troponin), and severity of AKI (as a categorical variable). Alpha risk was set at 0.05. All statistical analyses were performed on R V.4.0.4 (R Foundation for Statistical Computing).

Patient and public involvement

It was not appropriate to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Over a 4-year period, we retained the 3857 patients. Clinical characteristics are presented in [table 1](#). Briefly, 2905/3857 (75.0%) were men and median age was 70 (62; 77) years. Median EuroSCORE II was 1.68% (0.95–3.10).

Preoperative moderate to severe renal dysfunction, as defined per EuroSCORE II definitions, was present in 3153/3857 (82%) of patients. Peripheral arteriopathy prevalence was 509/3857 (13%), and 231/3857 (6%) of the operated patients were diabetic under insulin treatment. Cardiac surgery procedures included coronary artery bypass graft (CABG) in 2280/3857 (59%) of patients and isolated valve repair or replacement in 1577/3857 (54%) of patients. In-hospital mortality was 109/3857 (2.8%) (variables associated with mortality in unadjusted univariate survival analysis are detailed in online supplemental table 1).

Troponin analysis

After surgery, all patients showed troponin above the upper normal value, and 99.3% of them showed troponin above 10 times the upper normal value (troponin_{10N} hereafter). This precluded from assessing the sensitivity and predictive value towards mortality of troponin_{10N} threshold because of the imbalance between those who were above troponin_{10N} and other patients.

Cox regression model

In a time-dependent survival analysis, troponin was independently associated with mortality (per 1 ng/mL increase, adjusted HR (adj HR)=1.01; 95% CI 1.01 to 1.01, $p<0.001$) in a multivariable model adjusting for time-dependent creatinine, redo surgery and preoperative critical state (see [table 2](#)).

Peak troponin analysis

For sensitivity, the association between mortality and peak troponin was assessed in a multivariable analysis including preoperative creatinine, redo surgery and preoperative critical state. This analysis yielded similar results with

independent association between peak troponin and mortality (per 1 ng/mL increase, adj HR=1.01; 95% CI 1.01 to 1.01, $p<0.001$) (see [table 2](#)).

An ROC curve was drawn to assess discrimination feature of peak troponin, regarding in-hospital postoperative mortality (see [figure 1](#)). Its area under the curve was 0.74 (95% CI 0.69 to 0.80, $p<0.001$). Remarkably, a peak troponin higher than 100 times the upper normal value (labelled troponin_{100N} thereafter) was present in 45.5% of patients (1754/3857) and was significantly associated with an increase in mortality in univariate analysis (unadj HR=1.65; 95% CI 1.48 to 1.84, $p<0.001$), confirmed in multivariable analysis after adjusting for creatinine, preoperative critical state and redo surgery (adj HR=2.31; 95% CI 2.01 to 2.66, $p<0.001$) (see [table 2](#)). Mortality was 90/1754 (5.1%) among patients with peak troponin higher than troponin_{100N}. Troponin_{100N} was associated with a sensitivity of 82.57%, specificity of 55.60%, positive predictive value of 5.13% and negative predictive value of 99.10%, regarding subsequent in-hospital mortality.

Similarly, we assessed two other thresholds: troponin_{200N} and troponin_{500N}. Patients who reached these thresholds represented 977/3857 (25.3%) and 392/3857 (10.2%), respectively. Mortality was respectively 72/977 (7.4%) among patients with peak troponin higher than troponin_{200N} and 48/392 (12.2%) among patients with peak troponin higher than troponin_{500N}. These thresholds were significantly associated with in-hospital mortality (respective unadj HR 1.46 (95% CI 1.33 to 1.60) and 1.68 (95% CI 1.52 to 1.86)), confirmed in multivariable analysis (respective adj HR 1.75 (95% CI 1.57 to 1.94) and 1.57 (95% CI 1.41 to 1.75)). Details on models, sensitivity, specificity and predictive values are presented in online supplemental tables 2–4.

In a secondary analysis, we performed LCA which accounted for variations of troponin over time, assessing three paths with independent classes (see online supplemental figure 1), linked to a different prognosis (see [figure 2](#)). According to this model, event-free survival tended to be worse in patients with increasing troponin (2.2% of patients), compared with patients with stable (0.91% of patients) or decreasing troponin (96.9% of patients). Increasing troponin class was significantly associated with in-hospital mortality compared with the two other classes (HR 11.6; 95% CI 7.22 to 18.80).

Other biomarkers

Creatinine and renal function analysis

Peak creatinine was significantly associated with mortality in multivariable analysis including peak troponin, redo surgery and preoperative critical state (per 1 $\mu\text{mol/L}$ increase, adj HR=1.02; 95% CI 1.01 to 1.02, $p<0.001$) (see [table 3](#)). When considering AKI severity, mortality was increased for each class increase in AKIN/KDIGO (adj HR=2.83; 95% CI 2.63 to 3.03, $p<0.001$) (see [table 3](#)).

Table 1 Clinical and biological characteristics

	All patients (n=3857)	No event (n=3748)	Event (n=109)	Intergroup comparison P value
Demographic characteristics				
Women (%)	952 (25)	915 (24)	37 (34)	0.023
Age (years)	70 (62–77)	70 (62–77)	76 (68–83)	<0.001
Weight (kg)	77 (67–86)	77 (67–87)	73 (62–80)	0.006
Height (cm)	170 (165–176)	170 (165–176)	170 (160–174)	0.004
Biological characteristics				
Total bilirubin (μmol/L)	5.6 (4.0–8.0)	5.5 (4.0–7.9)	7.7 (5.0–11.4)	<0.001
C-reactive protein (mg/L)	4 (1–32)	4 (1–31)	13 (3–67)	<0.001
AST (μ/L)	22 (17–30)	22 (17–30)	30 (19–46)	<0.001
ALT (μ/L)	21 (15–33)	21 (15–32)	22 (13–37)	0.7
Baseline troponin (ng/mL)	0.7 (0.04–2.03)	0.7 (0.04–2.00)	0.61 (0.04–4.10)	0.3
Peak troponin (ng/mL)	2.43 (1.28–5.37)	2.37 (1.26–5.13)	8.44 (3.49–24.52)	<0.001
Baseline creatinine (μmol/L)	89 (76–105)	89 (76–105)	96 (80–131)	<0.001
EuroSCORE II characteristics				
EuroSCORE II	1.72 (0.97–3.23)	1.68 (0.95–3.10)	5.75 (2.93–13.86)	<0.001
Preoperative critical state (%)	47 (1.2)	30 (0.8)	17 (16)	<0.001
Non-programmed surgery (%)	517 (13)	483 (13)	34 (31)	<0.001
Redo surgery (%)	150/3857 (3.9)	134/3748 (3.6)	16/109 (15)	<0.001
Moderate left ventricle dysfunction (LVEF 31%–50%)	544/3857 (14%)	515/3748 (14%)	29/109 (27%)	<0.001
Severe left ventricle dysfunction (LVEF 21%–30%)	73/3857 (1.9%)	70/3748 (1.9%)	3/109 (2.8%)	0.5
Very severe left ventricle dysfunction (LVEF ≤20%)	8/3857 (0.2%)	6/3748 (0.2%)	2/109 (1.8%)	0.02
Postinfarction ventricular septal defect (%)	8/3857 (0.2)	4/3748 (0.1)	4/109 (3.7)	<0.001
Recent myocardial infarction (<3 months)	132/3857 (3.4%)	122/3748 (3.3%)	10/109 (9.2%)	0.004
Unstable angina (%)	16/3857 (0.4)	14/3748 (0.4)	2/109 (1.8)	0.073
Dyspnoea (%)				<0.001
NYHA 2	619 (16)	608 (16)	11 (10)	
NYHA 3	711 (18)	680 (18)	31 (28)	
NYHA 4	51 (1.3)	37 (1)	14 (13)	
Active endocarditis (%)	110/3857 (2.9)	98/3748 (2.6)	12/109 (11)	<0.001
Number of associated non-CABG procedures (%)				0.03
1	1212 (31)	1174 (31)	38 (35)	
2	682 (18)	649 (17)	33 (30)	
3	57 (1.5)	52 (1.4)	5 (4.6)	
Moderate kidney injury (eGFR 50–85 mL/min)	1973/3857 (51%)	1937/3748 (52%)	36/109 (33%)	<0.001
Severe kidney injury (eGFR <50 mL/min)	1180/3857 (31%)	1119/3748 (30%)	61/109 (56%)	<0.001
Haemodialysis (%)	52/3857 (1.3)	44/3748 (1.2)	8/109 (7.3)	<0.001
Peripheral arteriopathy (%)	509/3857 (13)	495/3748 (13)	14/109 (13%)	1.00
Diabetes (%)	231/3857 (6)	223/3748 (5.9)	8/109 (7.3)	0.5
COPD (%)	171/3857 (4.4)	160/3748 (4.3)	11/109 (10)	0.008
Moderate pulmonary arterial hypertension (<55 mm Hg)	996/3857 (26%)	960/3748 (26%)	36/109 (33%)	0.081

Continued

Table 1 Continued

	All patients (n=3857)	No event (n=3748)	Event (n=109)	Intergroup comparison P value
Severe pulmonary arterial hypertension (>55 mm Hg)	217/3857 (5.6%)	200/3748 (5.3%)	17/109 (16%)	<0.001
Reduced mobility (%)	56/3857 (1.5)	51/3748 (1.4)	5/109 (4.6)	0.02
Procedure characteristics				
Emergency surgery (%)	3/3857 (0.0007)	1/3748 (0.0002)	2/109 (1.8)	<0.001
Number of aortocoronary bypasses (%)				<0.001
0	1577/3857 (40.8)	1523/3748 (40.6)	54/109 (49.5)	
1	196/3857 (5.1)	184/3748 (4.9)	12/109 (11)	
2	812/3857 (21.1)	788/3748 (21)	24/109 (22)	
3 and more	1272/3857 (33)	1253/3748 (33.4)	19/109 (17.4)	
Aortic valve replacement (%)	1199/3857 (31)	1159/3748 (31)	40/109 (37)	0.2
Mitral valve replacement (%)	321/3857 (8.3)	296/3748 (7.9)	25/109 (23)	<0.001
Tricuspid valve repair (%)	177/3857 (4.6)	169/3748 (4.5)	8/109 (7.3)	0.2
Mitral valve repair (%)	375/3857 (9.7)	367/3748 (9.8)	8/109 (7.3)	0.4

Data are presented as number (percentage) and median (first quartile–third quartile).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Inflammation and liver function analysis

Serum CRP and total bilirubin levels were associated with mortality in univariate survival analysis with respective unadj HR=1.01 (95% CI 1.01 to 1.01) and 1.05 (95% CI 1.02 to 1.08), $p<0.001$ for both. However, these biomarkers were not independently associated with mortality, once accounting for troponin and serum creatinine. Meanwhile, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamate pyruvate

transaminase (SGPT) were not associated with in-hospital mortality.

DISCUSSION

The aim of our study was to assess the prognostic value of postoperative troponin and other routine care biomarkers in patients undergoing cardiac surgery using

Table 2 Analyses assessing the association between troponin and in-hospital mortality

	Unadjusted HR (95% CI)	Multivariable analysis HR (95% CI)	P value
Time-dependent survival analysis			
Troponin levels (per 1 ng/mL increase)	1.01 (1.01 to 1.01)	1.01 (1.01 to 1.02)	<0.001
Redo surgery	2.95 (2.29 to 3.80)	2.83 (1.35 to 5.94)	<0.001
Preoperative critical state	21.20 (13.77 to 32.64)	12.19 (5.91 to 25.14)	<0.001
Creatininemia (per 1 $\mu\text{mol/L}$ increase)	1.03 (1.03 to 1.04)	1.02 (1.01 to 1.03)	<0.001
Survival analysis (peak troponin and creatinine at baseline)			
Peak troponin (per 1 ng/mL increase)	1.01 (1.01 to 1.01)	1.01 (1.00 to 1.01)	<0.001
Redo surgery	3.25 (1.90 to 5.57)	2.75 (1.05 to 7.24)	<0.001
Preoperative critical state	7.12 (4.11 to 12.36)	9.69 (4.14 to 22.67)	<0.001
Creatinine at baseline (per 1 $\mu\text{mol/L}$ increase)	1.00 (1.00 to 1.01)	1.00 (1.00 to 1.01)	<0.001
100 times upper normal troponin value (troponin_{100N}) threshold survival analysis			
Above troponin _{100N} threshold	1.65 (1.48 to 1.84)	2.31 (2.01 to 2.66)	<0.001
Redo surgery	2.95 (2.29 to 3.80)	2.91 (2.45 to 3.45)	<0.001
Preoperative critical state	21.20 (13.77 to 32.64)	11.19 (9.42 to 13.30)	<0.001
Creatininemia (per 1 $\mu\text{mol/L}$ increase)	1.03 (1.03 to 1.04)	1.02 (1.02 to 1.03)	<0.001

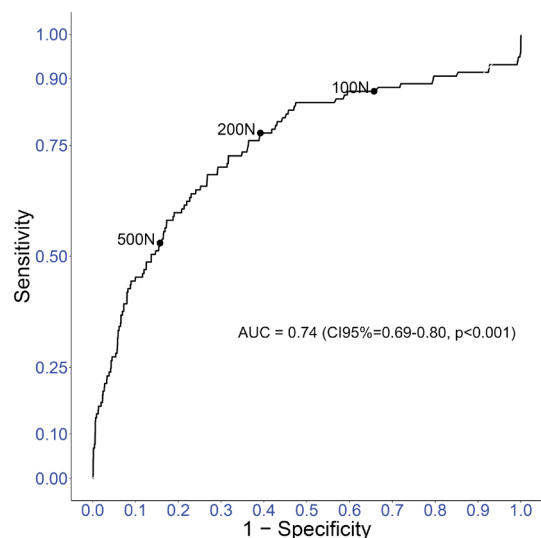


Figure 1 Receiver operating characteristic (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality. AUC, area under the curve.

time-dependent survival analyses adjusting for several confounding factors.

The main findings of our study are: (1) all patients develop a peak troponin after cardiac surgery above normal, and 99.3% above 10 times the upper normal value; (2) troponin, whether assessed as a single value, or as a time-dependent variable, was associated with in-hospital mortality; (3) this association remained significant after accounting for confounders which included renal function, inflammation and liver function; and (4) AKI severity was independently associated with mortality.

Assessing patients' severity is a daily task for cardiac surgery intensivists. Preoperative prognostication is a key step to validate surgery indications, prepare patients and anticipate adverse events. Risk scores such as EuroSCORE II are often used for preoperative risk assessment,^{18 19} and may be completed with other biomarkers, such as brain

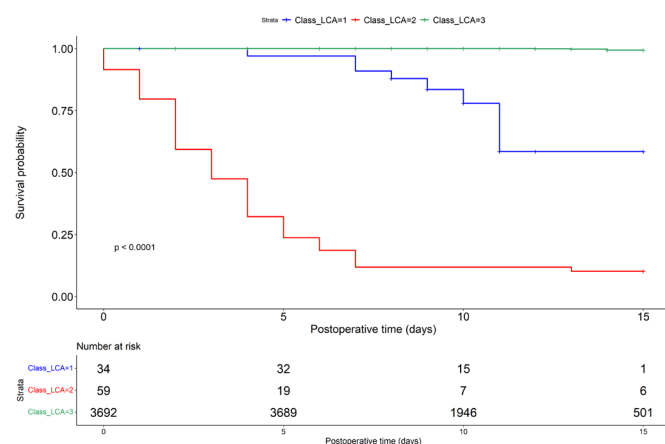


Figure 2 Survival curves depending on latent classes, regarding in-hospital mortality (censored at 15 days). Latent class analyses (LCA) are categorised as follows: (1) represent stable troponin, (2) represent increasing troponin, and (3) represent decreasing troponin trend.

natriuretic peptide in heart failure with preserved ejection fraction.^{20 21} Just as importantly, after surgery, patients are at high risk of developing adverse events related to the procedure, which include infections, circulatory failure, respiratory complications²² and, in a few cases, postprocedural myocardial infarction.²

The main issue lies in the definition of myocardial infarction. Cardiac troponin, I or T, is the injury's cornerstone, replacing old creatine kinase criterion. The injury threshold changed over time and studies such as the one we present. The European Society of Cardiology Joint Working Groups Position Paper² used several thresholds of peak troponin to define perioperative myocardial infarction: a peak troponin_{10N} with wall motion abnormalities or ECG dynamic modifications or any peak above troponin_{20N}. In 2018, myocardial injury was defined by joint work groups in a universal definition as an isolated cardiac troponin rise above troponin_{10N}.¹⁴

In our study, virtually all patients reached troponin_{10N} which confirms the fact that using such threshold in this specific population may not be adequate. Hence, our study comforts the definition given in the joint group position paper of 2017, more than that of the universal definition of type 5 myocardial infarction described in the 2018 paper.

Myocardial infarction is a common postoperative complication. Acute CABG occlusion or coronary ischaemia due to valve implantation is a curable event, for which diagnosis often requires multiparametric assessment, including ECG, echocardiography and troponin. Indeed, infarcted territory extension is correlated to troponin elevation.²³ Most importantly, prompt coronary angiography is required to definitively rule out myocardial infarction, but such an invasive examination would not be feasible if so many patients were defined as 'at high risk of coronary adverse event' due to troponin elevation only. Thus, a longitudinal evaluation of troponin emerges as an alternative solution to assess patient's prognostic and consider myocardial infarction diagnosis. Indeed, beyond analysing peak troponin, we confirmed that longitudinal analysis brought a different perspective to the myocardial injury assessment: patients with constant troponin decrease were at much lower risk of further mortality than those with stagnant or rising troponin.

We acknowledge that the prognostic value of troponin rise, reflecting cardiomyocyte supply/demand mismatch, has been established in non-cardiac surgery.⁴ Yet, it has less been studied in cardiac surgery.²⁴ The predictive value of troponin regarding sudden cardiac arrest has been shown²⁵ in a monocentric cohort of patients with valvular disease. A meta-analysis gathering 17 studies concluded in a strong correlation between postoperative troponin elevation and mortality in a CABG and valvular population (OR 5.46 for 30-day mortality). Koppen *et al* conducted a prospective cohort study with 626 isolated CABG, evaluating rise and full troponin T pattern-associated independent factors, highlighting low left ventricular ejection fraction, elevated New York Heart

Table 3 Analyses assessing the association between renal function and in-hospital mortality

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P value
Survival analysis (peak troponin and peak creatinine)			
Peak creatininemia (per 1 µmol/L increase)	1.02 (1.02 to 1.03)	1.02 (1.01 to 1.02)	<0.001
Peak troponin level (per 1 ng/mL increase)	1.01 (1.01 to 1.01)	1.01 (1.01 to 1.01)	<0.001
Preoperative critical state	7.12 (4.11 to 12.36)	4.40 (4.13 to 4.67)	<0.001
Redo surgery	3.25 (1.90 to 5.57)	2.26 (1.98 to 2.54)	<0.001
Survival analysis (peak troponin and AKIN)			
AKIN stage (per-1-stage-increase)	3.61 (3.42 to 3.80)	2.83 (2.63 to 3.03)	<0.001
Peak troponin level (per 1 ng/mL increase)	1.01 (1.01 to 1.01)	1.01 (1.01 to 1.01)	<0.001
Preoperative critical state	7.12 (4.11 to 12.36)	3.88 (3.62 to 4.14)	<0.001
Redo surgery	3.25 (1.90 to 5.57)	2.17 (1.91 to 2.43)	<0.001

AKIN, Acute Kidney Injury Network.

Association, inflammation biomarkers (CRP), creatinine and surgery duration as troponin variation explanation from a different perspective.¹⁰

The prognostic value of troponin variation may be explained by several mechanisms. The most obvious lies in myocardial infarctions, which could remain undiagnosed because of lack of ECG, echocardiographic and clinical element, but still be associated with lethal adverse complications (rhythmic and heart failure related). Second, myocardial injuries, be they due to surgeon lesion, ischaemia/reperfusion mechanism or cardioplegia dysfunction, are purveyors of inflammation, itself associated with poor outcomes.²⁶ Indeed, cardiomyocyte supply/demand mismatch may be secondary to inflammation as well as anaemia and hypotension. Indeed, troponin elevation is known to be closely related to renal dysfunction, inflammation and cardiac failure.¹⁰

Interestingly, in our cohort, inflammation (CRP) and hepatic dysfunction (aspartate amino transferase/alanine amino transferase and bilirubin) were not independently associated with mortality, once accounting for troponin and creatinine variations, which comforts the overarching strength of association between troponin and mortality.

Independent of troponin association with mortality, we also observed that creatinine was associated with mortality, whether in time-dependent survival, peak creatinine and AKI severity (as defined by AKIN/KDIGO) analyses. Indeed, acute renal failure has been regularly considered as a strong risk factor for death when defined as dialysis requirement,²⁷ Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) or AKIN criteria.^{28–30} Even minimal changes in creatinine as small as 0.5 mg/dL were found to be associated with 30-day mortality.³¹ However, similar to troponin, data on longitudinal values of creatinine are scarce and our work comforts these findings. Of note, in our study, mortality risk increase was lower than that previously reported whether in absolute peak creatinine elevation (2.8–4 times in previous studies for an elevation of 0.5 mg/dL³¹) or AKIN/KDIGO stage increase (5.3 times per each stage increase),³⁰ possibly due to less

severe overall patients (in our cohort, EuroSCORE II was 1.68 in patients who survived and 5.75 in those who died, compared with 5.5 and 8.4, respectively).³¹

The strengths of the present study include a longitudinal troponin measurement allowing a better evaluation of rise/fall, believed to be a better reflection of myocardial injury, a high number of inclusions and a homogeneous population with a systematic biological follow-up. We acknowledge several limitations to our study. A single-centred cohort has a limited external validation, though the population's characteristics appear to be representative of a standard cardiac surgery patient. The main outcome was in-hospital mortality, which is a variable criterion, but is frequently adopted in cardiac surgery studies. Our results only refer to cardiac I-troponin, yet it is believed to be more cardiac specific than T-troponin.^{32 33} For ethical reasons, we could not systematically perform coronary angiography after surgery; hence, cannot compute sensitivity and specificity towards myocardial infarction.

Our work is in line with several others, which found a high incidence of significant troponin elevation after cardiac surgery.^{34 35} More importantly, as recently highlighted, thresholds which define actual consensus on myocardial infarction may be too low to be clinically useful. A recent work published by Devereaux *et al*³⁶ showed the threshold associated with mortality requiring to be at least 218 times the upper normal value on the first day after surgery to be significantly associated with mortality. This high threshold is akin to that we observed in our study. Yet, a higher threshold, associated with variability parameters, may be more appropriate; yet, only a large multicentre prospective initiative with systematic coronary angiography may adequately answer this question.

CONCLUSION

In this cohort study, postoperative troponin was significantly associated with in-hospital mortality, whether analysed as a time-dependent (ie, longitudinal) or peak value

variable. Multivariable models adjusting for renal function, liver function, inflammatory syndrome and preoperative state comforted these findings. Of note, 99.3% of patients presented a peak ultrasensitive troponin above 10 times the upper normal value, questioning the relevance of this threshold to define postoperative myocardial infarctions after cardiac surgery.

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Contributors AC wrote the manuscript. AD performed the analyses. MS participated in data collection and provided critical review to the manuscript. LSN cowrote the manuscript, supervised this study and acts as the guarantor of this study.

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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 Not applicable.

Ethics approval This study involves human participants and was approved by an ethics committee and declared to the French-relevant organisation, Commission Nationale de l'Informatique et des Libertés (CNIL 2109982). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are subject to the French national legislation which requires the participating centres to adhere to its laws. Data may be exchanged after submitting adequate forms to the Commission Nationale de l'Informatique et des Libertés (CNIL).

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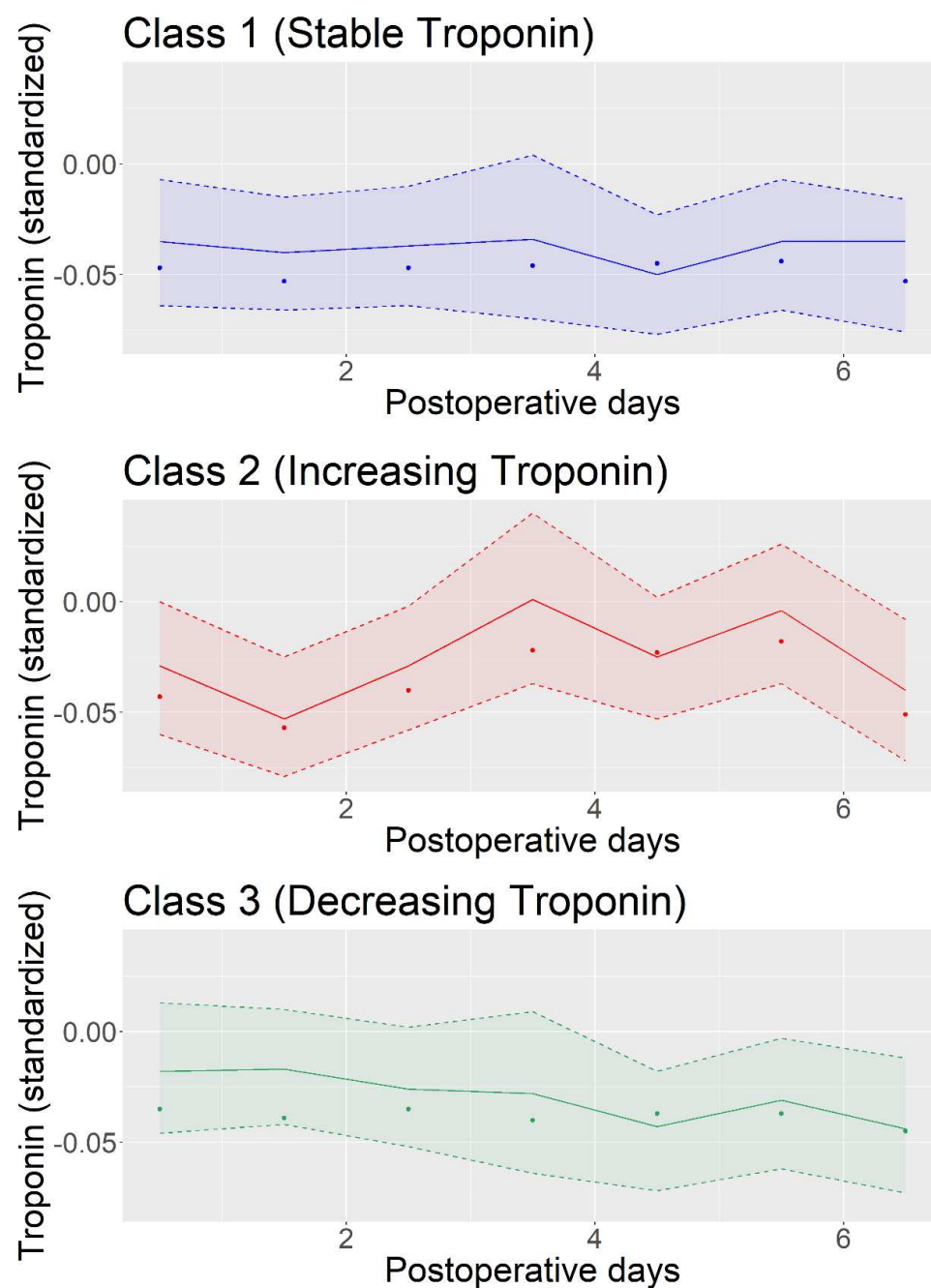
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Supplementary Material

Supplementary Figure 1. Troponin variation trajectories (latent classes) categorization. Latent classes (LCA) are categorized as follow: 1: represent stable troponin, 2: represent increasing troponin and 3: represent decreasing troponin trend.



Supplementary Table 1. Variables associated with in-hospital mortality in univariate survival analysis.

Variables	HR	95% CI inferior tail	95% CI superior tail	p-value
Total bilirubin (per-1- μ mol/L increase)	1.05	1.02	1.08	< 0.001
C-reactive protein (per-1-mg/mL increase)	1.01	1.01	1.01	< 0.001
Troponin (per-1-ng/mL increase)	1.01	1.01	1.01	< 0.001
Peak troponin (per-1-ng/mL increase)	1.01	1.01	1.01	< 0.001
Creatinine (per-1- μ mol/L increase)	1.01	1.01	1.01	< 0.001
Peak creatinine (per-1- μ mol/L increase)	1.02	1.02	1.03	< 0.001
Urgent surgery	7.43	4.32	12.78	< 0.001
Unprogrammed surgery	2.33	1.53	3.55	< 0.001
Rescue surgery	73.58	13.41	403.74	< 0.001
Mitral valve replacement	2.21	1.40	3.49	< 0.001
EuroScore 2 (per-1-unit increase)	1.10	1.02	1.18	0.011
Age (per-1-unit increase)	1.05	1.03	1.07	< 0.001
Moderate LV dysfunction (LVEF 31-50%)	1.85	1.19	2.85	0.006
Critical LV dysfunction (LVEF < 20%)	12.78	3.06	53.36	< 0.001
Redux	2.95	2.29	3.80	< 0.001
Severe AKI	2.45	1.66	3.62	< 0.001
Severe pulmonary hypertension	2.26	1.31	3.89	0.003
Recent myocardial infarction	2.30	1.52	5.79	0.001
Angina	6.33	1.56	25.78	0.01
Thoracic aorta surgery	2.36	1.27	4.39	0.007
Preoperative critical state	21.20	13.77	32.64	< 0.001
NYHA 3	1.58	1.03	2.43	0.036
NYHA 4	6.57	3.35	12.90	< 0.001
2 non-CABG associated procedures	1.61	1.06	2.46	0.026
3 non-CABG associated procedures	2.71	1.10	6.68	0.030
Post-infarction interventricular communication	9.46	2.72	32.95	< 0.001

Abbreviations : HR : hazard ratio ; CI : confidence interval ; LVEF : left ventricular ejection fraction; CABG: coronary artery bypass graft; AKI: acute kidney injury

Supplementary Table 2. Sensitivity, specificity, positive and negative predictive values associated with other thresholds of troponin levels, regarding in-hospital mortality.

Troponin_{XXN} refers to XX-times upper normal troponin value.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Troponin _{200N}	66.06%	75.85%	7.37%	98.72%
Troponin _{500N}	44.04%	90.82%	12.24%	98.24%

Supplementary Table 3. Multivariable analysis assessing the association between 200-times normal troponin threshold and in-hospital mortality.

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p
>Troponin _{200N}	1.46 (1.33 – 1.60)	1.75 (1.57 – 1.94)	< 0.001
Redux	2.95 (2.29 – 3.80)	1.12 (0.99 – 1.40)	0.07
Preoperative critical state	21.20 (13.77 – 32.64)	5.86 (4.93 – 6.98)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.03)	< 0.001

Supplementary Table 4. Multivariable analysis assessing the association between 500-times normal troponin threshold and in-hospital mortality.

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p
>Troponin _{500N}	1.68 (1.52 – 1.86)	1.57 (1.41 – 1.75)	< 0.001
Redux	2.95 (2.29 – 3.80)	0.98 (0.83 – 1.17)	0.84
Preoperative critical state	21.20 (13.77 – 32.64)	4.08 (3.40 – 4.88)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.03 (1.02 – 1.04)	< 0.001