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Incidence of type 5 myocardial infarction and prognostic value of troponin after cardiac surgery

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Incidence of type 5 myocardial infarction and prognostic value of troponin after cardiac surgery

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Abstract (250 words)

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 threshold values regarding the definition of myocardial infarction have been suggested. We aimed to confirm the accuracy of troponin, analyzed as time-dependent variable, to predict mortality, independently from other biomarkers; and to assess the incidence of type 5 myocardial infarction, as defined by the fourth universal definition.

Methods In a prospective cohort of patients who underwent cardiopulmonary bypass cardiac procedures, we assessed the association between serum levels of troponin, creatinine, bilirubin, SGOT, SGPT, CRP, lactate, and in-hospital mortality. Several models were tested, including time-dependent Cox regression, survival analysis with peak values 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 peak elevation above 10 times upper norm value occurred in 2532/3857, 65.6% of patients and was associated with a specificity of 34.7% and positive predictive value of 3.7% towards in-hospital mortality. 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 was independently associated with mortality after cardiac surgery. This association was independent from inflammatory syndrome, renal and liver failure. Furthermore, we observed that 65.6% of patients developed type 5 myocardial infarction definition.

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Article summary - Strengths and limitations of this study

-In this large prospective cohort, troponin was associated with in-hospital mortality, independently from all confounders, including renal function and inflammation.

-Overall, 65.1% of patients developed type 5 myocardial infarction as defined by the fourth universal definition (i.e. 10 times the upper norm value).

-Defining higher thresholds may yield better specificity, and trigger specific management such as coronary angiography when reached.

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Introduction

Cardiac surgery procedures have a higher risk of postoperative complications, including death, as compared to 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 cardiac injury. Its polypeptide structure differs from the sequence of skeletal troponins and rises in myocardial hypoxemia. It is routinely used for myocardial infarction diagnosis,[1] even after cardiac surgery.[2] It is also known to yield prognostic value as an independent factor of mortality in patients without myocardial infarction, in heart failure,[3] non-cardiac surgery,[4, 5, 6] and even in overall hospitalized population.[6]

After cardiac surgery, troponin has been associated with reliable prognostic value [7]. Previous studies analyzed troponin as a binary single-timepoint variable (i.e. elevated or not, at a pre-specified 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 [8]. 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 [9]. 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). Thus, type 5 myocardial infarction was defined in the fourth universal definition of 2018, albeit after coronary artery bypass graft procedures.[10]

In the present work, we accounted for repeated troponin levels 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

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assess the prognosis 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 frequent troponin rose above 10 times its upper normal value and analyzed the prognostic value of this threshold.

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Methods

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

Data come from the Registry for the Improvement of Postoperative Outcomes in Cardiac and Thoracic Surgery (RIPOSTE) database, registered at clinicaltrials.gov under NCT03209674. This registry was declared to the Commission nationale de l'informatique et des libertés (CNIL 2109982). The RIPOSTE database recorded prospectively patient's pre-operative and post-operative characteristics. Laboratory data were extracted concerning all in-hospital dosages of cardiac troponin, creatinine, lactate, transaminases, bilirubin, 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 EuroSCORE II, laboratory data, and in-hospital mortality. Echocardiographic parameters were prospectively collected in the database. Data were anonymized per national regulations and used with the approval of an institutional review board committee. Data collection was authorized 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 [11] Specifically, preoperative critical state referred to ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac

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massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support or preoperative acute renal failure (anuria or oliguria <10 ml/h). Redux surgery was defined as a history of cardiac surgery.

Biomarkers

Troponin. Cardiac I-troponin levels was measured with immunoanalysis ABBOT Architect I2000SR automaton, by CMIA (*chemiluminescent microparticle immunoassay).* Upper normal laboratory value was 0.16 ng/mL.

Creatininemia. Serum creatinine was assayed using enzymatic method with ABBOT 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-to-1.9-fold increase in creatinine or increase of more than 0.3mg/dL (26.5µmol/L). Stage 2: 2-to-2.9-fold increase from baseline. Stage 3 was defined as an elevation of more than 3 times compared to baseline or an increase to more than 4mg/dL (353.6µmol/L) and acute increase of more than 0.5mg/dL (44.2µmol/L).

Statistical analysis

Categorical variables were expressed as absolute number and percentage. Continuous variables were expressed as median and interquartile range (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, 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 optimize both Akaike information criterion (AIC), measuring the relative goodness-of-fit of the models,[12] and Bayesian information criterion (BIC) which penalizes model

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complexity more heavily,[13] 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 curves and by computing the area under curve (AUROC) with a 95% confidence interval (95%CI).

Additional analyses focused on peak troponin, instead of time-dependent troponin, using Cox regression models. Finally, we performed a latent class analysis 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 optimization of log-likelihood and BIC.

As secondary analyses, we focused on serum creatinine (as a continuous variable), observed as 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 version 4.0.4 (The R Foundation for Statistical Computing).

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Results

Over a 4-year period, we retained 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 CABG in 2280/3857, 59 % patients and isolated valve repair or replacement in 1577/3857, 54 % patients.

In-hospital mortality was 109/3857, 2.8% (variables associated with mortality in unadjusted univariate survival analysis are detailed in **Supplementary Table 1**).

Troponin analysis

Cox regression model. In a time-dependent survival analysis, troponin was independently associated with mortality (per 1-ng/mL-increase, adjusted hazard-ratio (adj.HR)=1.01 (CI95%=1.01-1.01, p<0.001) in a multivariable model adjusting for time-dependent creatinine, redux surgery, and preoperative critical state (see **Table 2a**).

Peak troponin analysis. For sensitivity, the association between mortality and peak troponin was assessed, in a multivariable analysis including pre-operative creatinine, redux surgery, and preoperative critical state. This analysis yielded similar results with independent association between peak troponin and mortality (per 1 ng/mL increase, adju.HR=1.01 (CI 95%=1.01-1.01, p<0.001)(see **Table 2b**).

A receiver operating characteristics (ROC) curve was drawn to assess discrimination feature of peak troponin, regarding in-hospital postoperative mortality (see **Figure 1**). Its area under the curve (AUC) was 0.74 (CI95%=0.69-0.80, p<0.001). Remarkably, a peak troponin higher than 10 times upper norm

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value (labeled troponin$_{10N}$ thereafter) was significantly associated with an increase in mortality in univariate analysis (unadj.HR=2.61 (CI 95%=1.48-1.53, p < 0.001), confirmed in multivariable analysis after adjusting for creatinine, preoperative critical state, and redux surgery (adj.HR=1.94 (CI95%=1.01=3.73, p=0.047)(see **Table 2c**). Troponin$_{10N}$ was present in 65.6% of patients (2532/3857) and was associated with a sensitivity of 86.9%, specificity of 34.7%, positive predictive value of 3.7% and negative predictive value of 98.9%, regarding subsequent in-hospital mortality.

Similarly, we assessed two other thresholds: troponin$_{20N}$ and troponin$_{50N}$. Patients who reached these thresholds represented 1535/3857, 39.8% and 636/3857, 16.5% respectively. They were also significantly associated with in-hospital mortality (respective unadj. HR 3.74 (CI 95%=2.38-5.89) and 4.27 (CI95%=2.89-6.31)), confirmed in multivariable analysis (respective adj. HR 3.86 (CI95%=2.23 – 6.69) and 3.74 (2.36 – 5.94). Details on models, sensitivity, specificity and predictive values, are presented in **Supplementary Tables 2, 3 and 4**.

In a secondary analysis, we performed latent class analysis which accounted for variations of troponin over time, assessing three paths with independent classes (see **Supplementary 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 to 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 to the two other classes (HR 11.6, CI95% 7.22-18.80).

Other biomarkers

Creatinine and renal function analysis. Peak creatinine was significantly associated with mortality in multivariable analysis including peak troponin, redux surgery and preoperative critical state (per-1-µmol/L-increase adj.HR=1.02 (CI 95%=1.01-1.02, p < 0.001)(see **Table 3a**). When considering AKI

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severity, mortality was increased for each class increase in AKIN/KDIGO (adj.HR=2.83 (CI95%=2.63-3.03, p < 0.001) (see **Table 3b**).

Inflammation and liver function analysis.

*S*erum CRP and total bilirubin levels were associated with mortality in univariate survival analysis with respective unadj.HR=1.01 (CI95%=1.01-1.01) and 1.05 (CI95%=1.02-1.08), p<0.001 for both. However, these biomarkers were not independently associated with mortality, once accounting for troponin and serum creatinine. Meanwhile, SGOT and SGPT were not associated with in-hospital mortality.

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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 time-dependent survival analyses adjusting for several cofounding factors.

The main findings of our study are: i) troponin, whether assessed as a single value, or as a time-dependent variable, was associated with in-hospital mortality; ii) this association remained significant after accounting for confounders which included renal function, inflammation, and liver function; iii) $troponin_{10N}$ was present in 65.6% of patients and was not as relevant as $troponin_{20N}$ regarding patients stratification for risk of mortality; and iv) 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,[14, 15] and may be completed with other biomarkers, such as brain natriuretic peptide in heart failure with preserved ejection fraction.[16, 17] Just as importantly, after surgery, patients are at high risk of developing adverse events related to the procedure, which include infections, circulatory failure, respiratory complications,[18] 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 CK definition. The injury threshold changed over time and studies such as the one we present. The ESC Joint WGs position paper,[2] used several threshold 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 the ESC universal definition as an isolated cardiac troponin rise above $troponin_{10N}$.[19]

In our study, 65.9% patients reached $troponin_{10N}$ which corresponded to a poor specificity towards in-hospital mortality (34.7%). Meanwhile, $troponin_{20N}$ occurred in 1535/3857 patients, 39.8%, and had

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better specificity towards in-hospital mortality. 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 post-operative complication. Acute CABG occlusion or coronary ischemia 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.[20] Most importantly, prompt coronary angiography is required to definitively rule out myocardial infarction, but such an invasive exam 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 analyzing 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 prognostic value of troponin rise, reflecting cardiomyocytes supply/demand mismatch has been established in non-cardiac surgery.[4] Yet, it has less been studied in cardiac surgery.[21] The predictive value of troponin regarding sudden cardiac arrest has been shown [22] in a monocentric cohort of patients with valvular disease. A meta-analysis gathering 17 studies concluded in a strong correlation between post-operative troponin elevation and mortality in a CABG and valvular population (OR 5.46 for 30-days mortality).(9) 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 Ventricle Ejection Fraction (LVEF), elevated NYHA, inflammation biomarkers (CRP), creatinine and surgery duration as troponin variation explanation, from a different perspective.[9]

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The explanation of the prognostic value of troponin variation is multiple. 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 injury, be they due to surgeon lesion, ischemia/reperfusion mechanism, cardioplegia dysfunction; all are purveyors of inflammation, itself associated with poor outcomes [23]. Indeed, cardiomyocyte supply/demand mismatch is a reliable witness of inflammation, but also anemia, hypotension, as many prognosis factors, helping the clinician assessing a day to day follow up. Indeed, troponin elevation is known to be closely related to renal dysfunction, inflammation, and cardiac failure [9]. Interestingly, in our cohort, inflammation (CRP) and hepatic dysfunction (ASAT/ALAT 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.

Independently from 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 [24], RIFLE or AKIN criteria [25, 26, 27]. Even minimal changes in creatinine as small as 0.5 mg/dL was found to be associated with 30-days mortality [28]. However, similarly 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 to 4 times in previous studies for an elevation of 0.5mg/dL [28]) or AKIN/KDIGO stage increase (5.3 times per each stage increase),[27] 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 to 5.5 and 8.4, respectively).[28]

The present study strengths include a longitudinal troponin measurement allowing a better evaluation of rise/fall, believed to be a better reflect of myocardial injury, a high number of

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inclusions, a homogeneous population with a systematic biological follow-up. We acknowledge several limitations to our study. A single centered cohort has a limited external validation, though the population's characteristics appear to be representative of a standard cardiac surgery patient. 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 [29, 30]. For ethical reasons, we could not systematically perform coronary angiography after surgery, hence, cannot compute sensitivity and specificity towards myocardial infarction.

Yet, in-hospital mortality in patients undergoing cardiac surgery remains highly associated with rising troponin and significant peak troponin, for which an adequate threshold remains to be determined, although 10N may not be specific enough, hence, not appropriate to rule out coronary adverse events.

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Conclusion

In this cohort study, postoperative troponin was significantly associated with in-hospital mortality, whether analyzed as a time-dependent (i.e. longitudinal) or peak value variable. Multivariable models adjusting for renal function, liver function, inflammatory syndrome and preoperative state comforted these findings. Of note, 65.6% patients presented a peak troponin above 10-times upper norm value, questioning the relevance of this threshold to define postoperative myocardial infarctions after cardiac surgery.

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Contributorship statement. A. Clement wrote the manuscript, A. Daulasim performed analyses, M. Souibri participated to data collection and provided critical review to the manuscript and L.S. Nguyen cowrote the manuscript and supervised this study.

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Competing interests: none

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

Ethics Approval. This study was approved by an Ethics committee and declared to the French relevant organism, Commission nationale de l'informatique et des libertés (CNIL 2109982).

Data sharing statement. Data may be shared upon reasonable request.

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Figures legend and Tables

Figure 1. Receiver Operator Characteristics (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality

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

Table 1. Clinical and biological characteristics

Table 2. Troponin analyses

Table 3. Renal function analyses

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 mortality in unadjusted univariate survival analysis

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

Supplementary Table 3.

Supplementary Table 4.

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Table 1 : clinical and biological characteristics

	All patients (N = 3857)	No event (N = 3748)	Event (N = 109)
Demographic characteristics			
Women	952 (25%)	915 (24%)	37 (34%)
Age, years	70 (62 – 77)	70 (62 – 77)	76 (68 – 83)
Weight, kg	77 (67 – 86)	77 (67 – 87)	73 (62 – 80)
Height, cm	170 (165 – 176)	170 (165 – 176)	170 (160 – 174)
Biological characteristics			
Total bilirubin, µmol/L	5.6 (4.0 – 8.0)	5.5 (4.0 – 7.9)	7.7 (5.0 – 11.4)
C-reactive protein, mg/L	4 (1 – 32)	4 (1 – 31)	13 (3 – 67)
AST, u/L	22 (17 – 30)	22 (17 – 30)	30 (19 – 46)
ALT, u/L	21 (15 – 33)	21 (15 – 32)	22 (13 – 37)
Baseline troponin, ng/L	0.7 (0.04 – 2.03)	0.7 (0.04 – 2.00)	0.61 (0.04 – 4.10)
Peak troponin, ng/L	2.43 (1.28 – 5.37)	2.37 (1.26 – 5.13)	8.44 (3.49 – 24.52)
Baseline creatinine, µmol/L	89 (76 – 105)	89 (76 – 105)	96 (80 – 131)
EuroSCORE II characteristics			
EuroSCORE II	1.72 (0.97 – 3.23)	1.68 (0.95 – 3.10)	5.75 (2.93 – 13.86)
Pre-operative critical state	47 (1.2%)	30 (0.8%)	17 (16%)
Non-programmed surgery	517 (13%)	483 (13%)	34 (31%)
Redux surgery	150/3857 (3.9%)	134/3748 (3.6%)	16/109 (15%)
Moderate left ventricle dysfunction (LVEF 31 – 50%)	544/3857 (14%)	515/3748 (14%)	29/109 (27%)
Severe left ventricle dysfunction (LVEF (21 - 30%)	73/3857 (1.9%)	70/3748 (1.9%)	3/109 (2.8%)
Very severe left ventricle dysfunction (LVEF ≤ 20%)	8/3857 (0.2%)	6/3748 (0.2%)	2/109 (1.8%)
Post-infarction ventricular septal defect	8/3857 (0.2%)	4/3748 (0.1%)	4/109 (3.7%)
Recent myocardial infarction (< 3 months)	132/3857 (3.4%)	122/3748 (3.3%)	10/109 (9.2%)
Unstable angina	16/3857 (0.4%)	14/3748 (0.4%)	2/109 (1.8%)
Dyspnea NYHA 2 NYHA 3 NYHA 4	 619 (16%) 711 (18%) 51 (1.3%)	 608 (16%) 680 (18%) 37 (1%)	 11 (10%) 31 (28%) 14 (13%)
Active endocarditis	110/3857 (2.9%)	98/3748 (2.6%)	12/109 (11%)

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Number of associated non-CABG procedures 1 2 3	 1212 (31%) 682 (18%) 57 (1.5%)	 1174 (31%) 649 (17%) 52 (1.4%)	 38 (35%) 33 (30%) 5 (4.6%)
Moderate kidney injury (eGFR 50 – 85mL/min)	1973/3857 (51%)	1937/3748 (52%)	36/109 (33%)
Severe kidney injury (eGFR < 50mL/min)	1180/3857 (31%)	1119/3748 (30%)	61/109 (56%)
Hemodialysis	52/3857 (1.3%)	44/3748 (1.2%)	8/109 (7.3%)
Peripheral arteriopathy	509/3857 (13%)	495/3748 (13%)	14/109 (13%)
Diabetes	231/3857 (6%)	223/3748 (5.9%)	8/109 (7.3%)
COPD	171/3857 (4.4%)	160/3748 (4.3%)	11/109 (10%)
Moderate pulmonary arterial hypertension (< 55mmHg)	996/3857 (26%)	960/3748 (26%)	36/109 (33%)
Severe pulmonary arterial hypertension (> 55mmHg)	217/3857 (5.6%)	200/3748 (5.3%)	17/109 (16%)
Reduced mobility	56/3857 (1.5%)	51/3748 (1.4%)	5/109 (4.6%)
Procedure characteristics			
Emergency surgery	3/3857 (0.0007%)	1/3748 (0.0002%)	2/109 (1.8%)
Number of aorto-coronary bypasses 0 1 2 3 and more	 1577/3857 (40.8%) 196/3857 (5.1%) 812/3857 (21.1%) 1272/3857 (33%)	 1523/3748 (40.6%) 184/3748 (4.9%) 788/3748 (21%) 1253/3748 (33.4%)	 54/109 (49.5%) 12/109 (11%) 24/109 (22%) 19/109 (17.4%)
Aortic valve replacement	1199/3857 (31%)	1159/3748 (31%)	40/109 (37%)
Mitral valve replacement	321/3857 (8.3%)	296/3748 (7.9%)	25/109 (23%)
Tricuspid valve repair	177/3857 (4.6%)	169/3748 (4.5%)	8/109 (7.3%)
Mitral valve repair	375/3857 (9.7%)	367/3748 (9.8%)	8/109 (7.3%)

Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, COPD = Chronic Obstructive Pulmonary Disease, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction

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Table 2 Troponin analyses

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p-value
Time-dependent survival analysis			
Troponin	1.01 (1.01 – 1.01)	1.01 (1.01 – 1.02)	< 0.001
Redux	2.95 (2.29 – 3.80)	2.83 (1.35 – 5.94)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	12.19 (5.91 – 25.14)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.03)	< 0.001
Survival analysis (peak troponin & creatinine at baseline)			
Peak troponin	1.01 (1.01 – 1.01)	1.01 (1.00 – 1.01)	< 0.001
Redux	3.25 (1.90 – 5.57)	2.75 (1.05 – 7.24)	< 0.001
Preoperative critical state	7.12 (4.11 – 12.36)	9.69 (4.14 – 22.67)	< 0.001
Creatinine at baseline	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)	< 0.001
10-times upper normal troponin value ($troponin_{10N}$) threshold survival analysis			
$Troponin_{10N}$	2.61 (1.48 – 1.53)	1.94 (1.01 – 3.73)	0.047
Redux	2.95 (2.29 – 3.80)	2.68 (1.37 – 5.25)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	7.87 (3.91 – 15.87)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.03 (1.01 – 1.04)	0.004

Table 3 Renal function analyses

	Unadjusted HR (95% IC)	Adjusted HR (95% IC)	p-value
Survival analysis (peak troponin & peak creatinine)			
Peak creatinine	1.02 (1.02 – 1.03)	1.02 (1.01 – 1.02)	< 0.001
Peak troponin	1.01 (1.01 – 1.01)	1.01 (1.01 – 1.01)	< 0.001
Preoperative critical state	7.12 (4.11 – 12.36)	4.40 (4.13 – 4.67)	< 0.001
Redux	3.25 (1.90 – 5.57)	2.26 (1.98 – 2.54)	< 0.001
Survival analysis (peak troponin & AKIN)			
AKIN stage (per 1-increase)	3.61 (3.42 – 3.80)	2.83 (2.63 – 3.03)	< 0.001
Peak troponin	1.01 (1.01 – 1.01)	1.01 (1.01 – 1.01)	< 0.001
Preoperative critical state	7.12 (4.11 – 12.36)	3.88 (3.62 – 4.14)	< 0.001
Redux	3.25 (1.90 – 5.57)	2.17 (1.91 – 2.43)	< 0.001

Abbreviations: AKIN: acute kidney injury network

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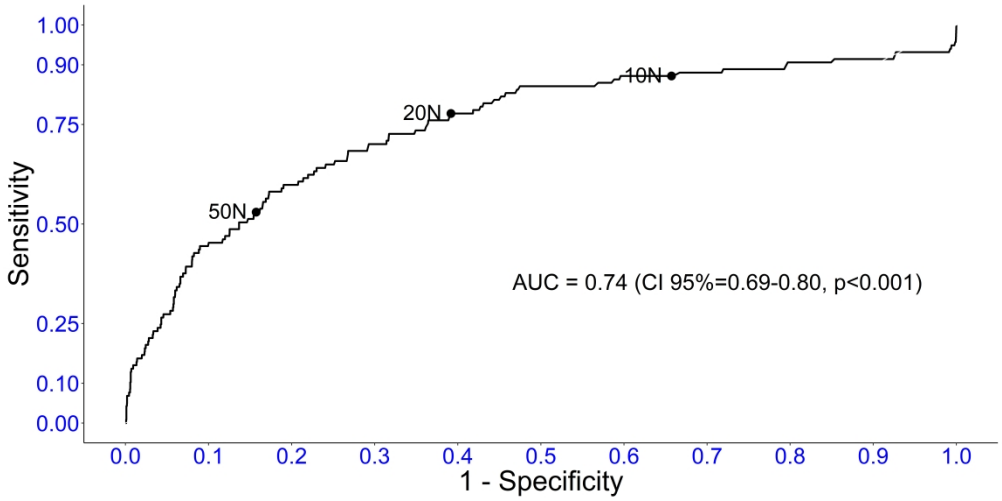

Figure 1. Receiver Operator Characteristics (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality

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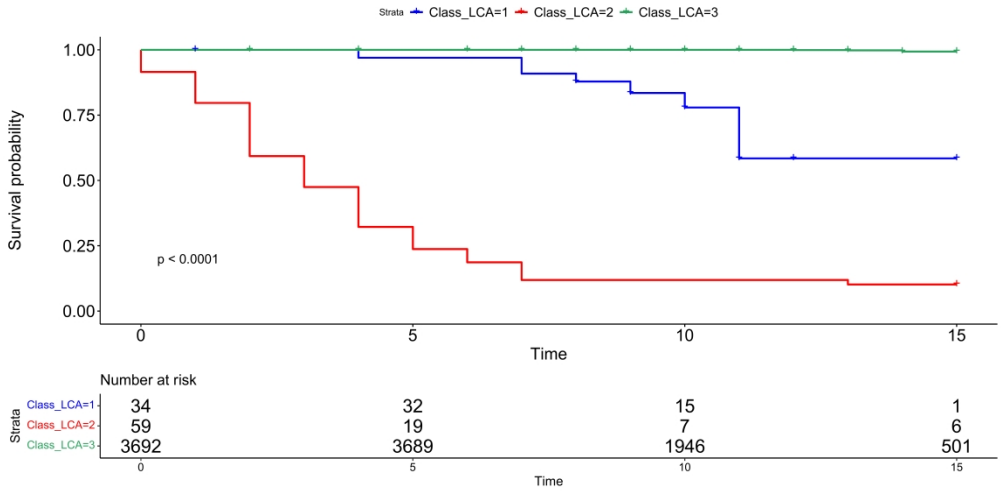

Figure 2. Survival curves depending on latent classes, regarding in-hospital mortality (censored at 15 days). Latent classes (LCA) are categorized as follow: 1: represent stable troponin, 2: represent increasing troponin and 3: represent decreasing troponin trend.

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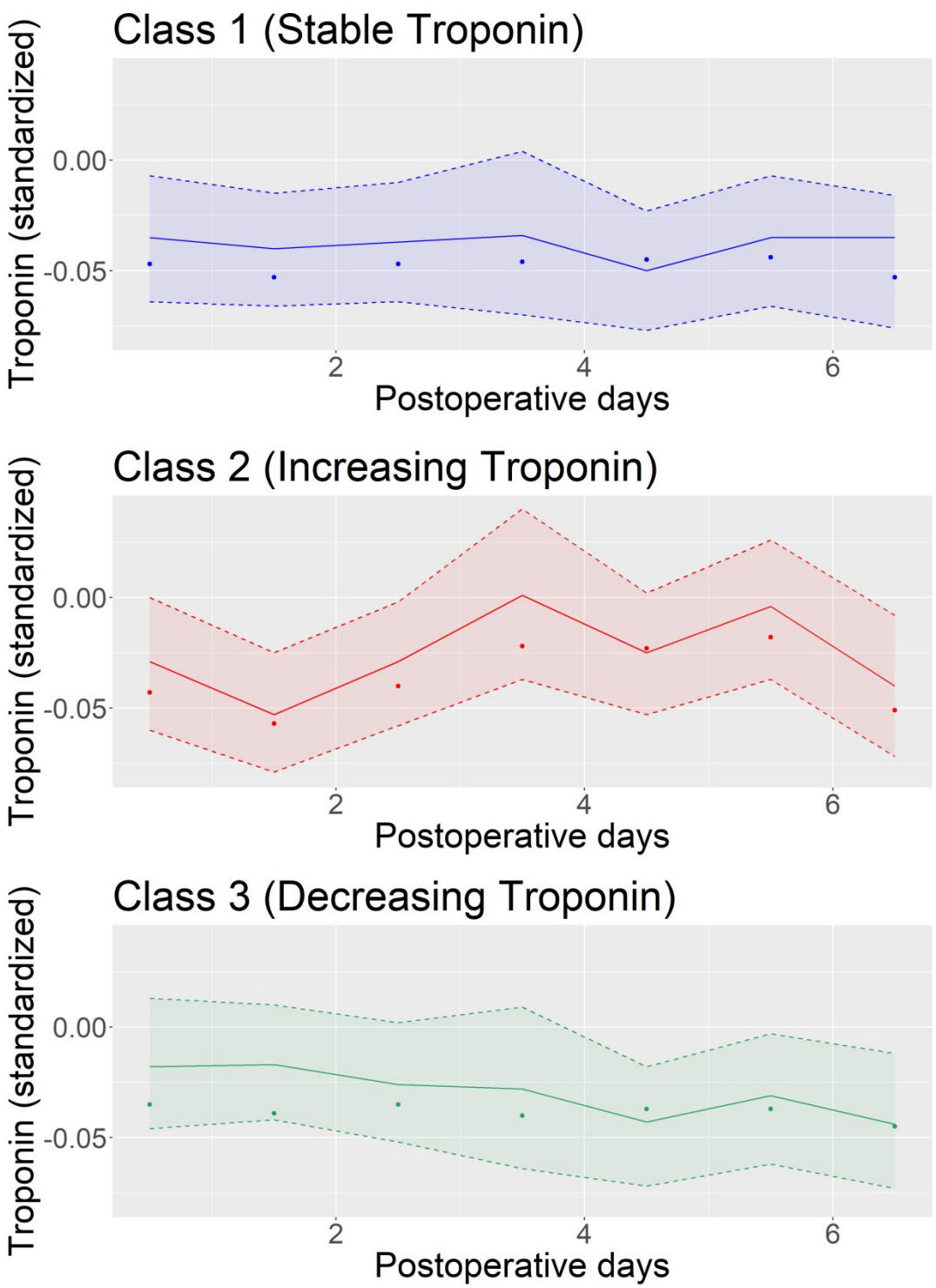
Supplementary Material

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.



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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-unit increase)	1.05	1.02	1.08	< 0.001
C-reactive protein (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Troponin (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Peak troponin (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Creatinine (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Peak creatinine (per-1-unit 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

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

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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$_{20N}$ (=3.2 ng/mL)	76.64%	61.09%	5.34%	98.92%
Troponin$_{50N}$ (=8 ng/mL)	52.34%	84.47%	8.81%	98.41%

Supplementary Table 3. 20-times normal troponin threshold survival analysis

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p
> 20 times upper norm value of troponin	3.74 (2.38 – 5.89)	3.86 (2.23 – 6.69)	< 0.001
Redux	2.95 (2.29 – 3.80)	2.38 (1.22 – 4.64)	0.011
Preoperative critical state	21.20 (13.77 – 32.64)	7.10 (3.53 – 14.25)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.04)	< 0.001

Supplementary Table 4. 50-times normal troponin threshold survival analysis

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p
> 50 times upper norm value of troponin	4.27 (2.89 – 6.31)	3.74 (2.36 – 5.94)	< 0.001
Redux	2.95 (2.29 – 3.80)	2.45 (1.25 – 4.78)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	6.12 (3.04 – 12.32)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.04)	< 0.001

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Incidence of troponin elevation and its prognostic value after cardiac surgery

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Incidence of troponin elevation and its prognostic value after cardiac surgery

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Abstract (250 words)

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, analyzed as time-dependent variable, to predict mortality, independently from other biomarkers; and to assess the incidence and prognosis of a 10-times-upper-norm-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, SGOT, SGPT, 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 2532/3857, 65.6% of patients and was associated with a specificity of 34.7% and positive predictive value of 3.7% towards in-hospital mortality. 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 was independently associated with mortality after cardiac surgery. This association was independent from inflammatory syndrome, renal and liver failure. $Troponin_{10N}$ was reached in 65.6% of patients, questioning the relevance of this criteria to define postoperative myocardial infarctions after cardiac surgery.

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Article summary - Strengths and limitations of this study

-In this large prospective cohort, troponin was associated with in-hospital mortality, independently from all confounders, including renal function and inflammation.

-Overall, 65.1% of patients presented at least 10-times upper-norm-value troponin elevation, which may correspond to type 5 myocardial infarction, as defined by the fourth universal definition.

-Defining higher thresholds may yield better specificity and trigger specific management such as coronary angiography when reached.

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Introduction

Cardiac surgery procedures have a higher risk of postoperative complications, including death, as compared to 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 cardiac injury. Its polypeptide structure differs from the sequence of skeletal troponins and rises in myocardial hypoxemia. It is routinely used for myocardial infarction diagnosis,[1] even after cardiac surgery.[2] It is also known to yield 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 hospitalized population.[6]

After cardiac surgery, troponin has been associated with reliable prognostic value.[7 8] Previous studies analyzed troponin as a binary single-timepoint variable (i.e. elevated or not, at a pre-specified 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-norm-value is common to several, including the fourth universal definition of myocardial infarction.

In the present work, we accounted for repeated troponin levels 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

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assess the prognosis 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 analyzed the prognostic value of this threshold.

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Methods

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

Data came from the Registry for the Improvement of Postoperative Outcomes in Cardiac and Thoracic Surgery (RIPOSTE) database, registered at clinicaltrials.gov under NCT03209674. This registry was declared to the Commission nationale de l'informatique et des libertés (CNIL 2109982). The RIPOSTE database recorded prospectively patient's pre-operative and post-operative characteristics. Laboratory data were extracted; they included all in-hospital levels of cardiac troponin, creatinine, lactate, transaminases, bilirubin, 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 EuroSCORE II, laboratory data, and in-hospital mortality. Echocardiographic parameters were prospectively collected in the database. Data were anonymized per national regulations and used with the approval of an institutional review board committee. Data collection was authorized 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,

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preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support or preoperative acute renal failure (anuria or oliguria <10 ml/h). Redo surgery was defined as a history of cardiac surgery.

Biomarkers

Troponin. Cardiac I-troponin levels was measured with immunoanalysis ABBOT Architect I2000SR automaton, by CMIA (*chemiluminescent microparticle immunoassay).* Upper normal laboratory value was 0.16 ng/mL, as stated by the manufacturer.

Creatininemia. Serum creatinine was assayed using enzymatic method with ABBOT 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-to-1.9-fold increase in creatinine or increase of more than 0.3mg/dL (26.5µmol/L). Stage 2: 2-to-2.9-fold increase from baseline. Stage 3 was defined as an elevation of more than 3 times compared to baseline or an increase to more than 4mg/dL (353.6µmol/L) and acute increase of more than 0.5mg/dL (44.2µmol/L).

Statistical analysis

Categorical variables were expressed as absolute number and percentage. Continuous variables were expressed as median and interquartile range (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, 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 optimize both Akaike information criterion (AIC), measuring the relative goodness-of-fit of the models,[16] and Bayesian information criterion (BIC) which penalizes model

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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 curves and by computing the area under curve (AUROC) with a 95% confidence interval (95%CI).

Additional analyses focused on peak troponin, instead of time-dependent troponin, using Cox regression models. Finally, we performed a latent class analysis 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 optimization of log-likelihood and BIC.

As secondary analyses, we focused on serum creatinine (as a continuous variable), observed as 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 version 4.0.4 (The R Foundation for Statistical Computing).

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Results

Over a 4-year period, we retained 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 CABG in 2280/3857, 59 % patients and isolated valve repair or replacement in 1577/3857, 54 % patients.

In-hospital mortality was 109/3857, 2.8% (variables associated with mortality in unadjusted univariate survival analysis are detailed in **Supplementary Table 1**).

Troponin analysis

Cox regression model. In a time-dependent survival analysis, troponin was independently associated with mortality (per 1-ng/mL-increase, adjusted hazard-ratio (adj.HR)=1.01 (CI95%=1.01-1.01, p<0.001) in a multivariable model adjusting for time-dependent creatinine, Redo surgery, and preoperative critical state (see **Table 2a**).

Peak troponin analysis. For sensitivity, the association between mortality and peak troponin was assessed, in a multivariable analysis including pre-operative 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, adju.HR=1.01 (CI 95%=1.01-1.01, p<0.001)(see **Table 2b**).

A receiver operating characteristics (ROC) curve was drawn to assess discrimination feature of peak troponin, regarding in-hospital postoperative mortality (see **Figure 1**). Its area under the curve (AUC) was 0.74 (CI95%=0.69-0.80, p<0.001). Remarkably, a peak troponin higher than 10 times upper norm

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value (labeled troponin$_{10N}$ thereafter) was significantly associated with an increase in mortality in univariate analysis (unadj.HR=2.61 (CI 95%=1.48-1.53, p < 0.001), confirmed in multivariable analysis after adjusting for creatinine, preoperative critical state, and redo surgery (adj.HR=1.94 (CI95%=1.01=3.73, p=0.047)(see **Table 2c**). Troponin$_{10N}$ was present in 65.6% of patients (2532/3857) and was associated with a sensitivity of 86.9%, specificity of 34.7%, positive predictive value of 3.7% and negative predictive value of 98.9%, regarding subsequent in-hospital mortality.

Similarly, we assessed two other thresholds: troponin$_{20N}$ and troponin$_{50N}$. Patients who reached these thresholds represented 1535/3857, 39.8% and 636/3857, 16.5% respectively. They were also significantly associated with in-hospital mortality (respective unadj. HR 3.74 (CI 95%=2.38-5.89) and 4.27 (CI95%=2.89-6.31)), confirmed in multivariable analysis (respective adj. HR 3.86 (CI95%=2.23 – 6.69) and 3.74 (2.36 – 5.94). Details on models, sensitivity, specificity and predictive values, are presented in **Supplementary Tables 2, 3 and 4**.

In a secondary analysis, we performed latent class analysis which accounted for variations of troponin over time, assessing three paths with independent classes (see **Supplementary 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 to 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 to the two other classes (HR 11.6, CI95% 7.22-18.80).

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-µmol/L-increase adj.HR=1.02 (CI 95%=1.01-1.02, p < 0.001)(see **Table 3a**). When considering AKI

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severity, mortality was increased for each class increase in AKIN/KDIGO (adj.HR=2.83 (CI95%=2.63-3.03, p < 0.001) (see **Table 3b**).

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 (CI95%=1.01-1.01) and 1.05 (CI95%=1.02-1.08), p<0.001 for both. However, these biomarkers were not independently associated with mortality, once accounting for troponin and serum creatinine. Meanwhile, SGOT and SGPT were not associated with in-hospital mortality.

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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 time-dependent survival analyses adjusting for several cofounding factors.

The main findings of our study are: i) troponin, whether assessed as a single value, or as a time-dependent variable, was associated with in-hospital mortality; ii) this association remained significant after accounting for confounders which included renal function, inflammation, and liver function; iii) $troponin_{10N}$ was present in 65.6% of patients and was not as relevant as $troponin_{20N}$ regarding patients stratification for risk of mortality; and iv) 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 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 complications,[22] 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 CK definition. The injury threshold changed over time and studies such as the one we present. The ESC Joint WGs position paper,[2] used several threshold 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, 65.9% patients reached $troponin_{10N}$ which corresponded to a poor specificity towards in-hospital mortality (34.7%). Meanwhile, $troponin_{20N}$ occurred in 1535/3857 patients, 39.8%, and had

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better specificity towards in-hospital mortality. 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 post-operative complication. Acute CABG occlusion or coronary ischemia 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 exam 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 analyzing 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 prognostic value of troponin rise, reflecting cardiomyocytes 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 shown [25] in a monocentric cohort of patients with valvular disease. A meta-analysis gathering 17 studies concluded in a strong correlation between post-operative troponin elevation and mortality in a CABG and valvular population (OR 5.46 for 30-days 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 Ventricle Ejection Fraction (LVEF), elevated NYHA, inflammation biomarkers (CRP), creatinine and surgery duration as troponin variation explanation, from a different perspective.[10]

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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, ischemia/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 anemia 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 (ASAT/ALAT 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.

Independently from 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], RIFLE or AKIN criteria [28-30]. Even minimal changes in creatinine as small as 0.5 mg/dL was found to be associated with 30-days mortality [31]. However, similarly 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 to 4 times in previous studies for an elevation of 0.5mg/dL [31]) 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 to 5.5 and 8.4, respectively).[31]

The present study strengths include a longitudinal troponin measurement allowing a better evaluation of rise/fall, believed to be a better reflect of myocardial injury, a high number of inclusions, a homogeneous population with a systematic biological follow-up. We acknowledge

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several limitations to our study. A single centered cohort has a limited external validation, though the population's characteristics appear to be representative of a standard cardiac surgery patient. 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. While in our work, we used a standard troponin assay and found a significant independent association between a $troponin_{10N}$ threshold and mortality, specificity remained low (34.7%) as well as positive predictive value (3.7%). Even more are assays based on high-sensitive troponin, for which the recent work published by Devereaux et al. showed that the threshold associated with mortality requiring to be at least 218 times the upper-norm-value on the first day after surgery to be significantly associated with mortality.[36] A more elevated threshold, associated with variability parameters, may be more appropriate, yet, only a large multicenter prospective initiative with systematic coronary angiography may adequately answer this question.

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Conclusion

In this cohort study, postoperative troponin was significantly associated with in-hospital mortality, whether analyzed as a time-dependent (i.e. longitudinal) or peak value variable. Multivariable models adjusting for renal function, liver function, inflammatory syndrome and preoperative state comforted these findings. Of note, 65.6% patients presented a peak troponin above 10-times upper norm value, questioning the relevance of this threshold to define postoperative myocardial infarctions after cardiac surgery.

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Contributorship statement. A. Clement wrote the manuscript, A. Daulasim performed analyses, M. Souibri participated to data collection and provided critical review to the manuscript and L.S. Nguyen cowrote the manuscript and supervised this study.

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Competing interests: none

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

Ethics Approval. This study was approved by an Ethics committee and declared to the French relevant organism, Commission nationale de l'informatique et des libertés (CNIL 2109982).

Data sharing statement. Data may be shared upon reasonable request.

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Figures legend and Tables

Figure 1. Receiver Operator Characteristics (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality

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

Table 1. Clinical and biological characteristics

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

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

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 mortality in unadjusted univariate survival analysis

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

Supplementary Table 3. Multivariable analysis assessing the association between 20-times normal troponin threshold and in-hospital mortality.

Supplementary Table 4. Multivariable analysis assessing the association between 50-times normal troponin threshold and in-hospital mortality.

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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, u/L	**22 (17 – 30)**	**22 (17 – 30)**	**30 (19 – 46)**	**< 0.001**
ALT, u/L	21 (15 – 33)	21 (15 – 32)	22 (13 – 37)	0.7
Baseline troponin, ng/L	0.7 (0.04 – 2.03)	0.7 (0.04 – 2.00)	0.61 (0.04 – 4.10)	0.3
Peak troponin, ng/L	**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**
Pre-operative 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**
Post-infarction 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
Dyspnea **NYHA 2** **NYHA 3** **NYHA 4**	 **619 (16%)** **711 (18%)** **51 (1.3%)**	 **608 (16%)** **680 (18%)** **37 (1%)**	 **11 (10%)** **31 (28%)** **14 (13%)**	**< 0.001**
Active endocarditis	**110/3857 (2.9%)**	**98/3748 (2.6%)**	**12/109 (11%)**	**< 0.001**

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Number of associated non-CABG procedures **1** **2** **3**	 **1212 (31%)** **682 (18%)** **57 (1.5%)**	 **1174 (31%)** **649 (17%)** **52 (1.4%)**	 **38 (35%)** **33 (30%)** **5 (4.6%)**	**0.03**
Moderate kidney injury (eGFR 50 – 85mL/min)	**1973/3857 (51%)**	**1937/3748 (52%)**	**36/109 (33%)**	**< 0.001**
Severe kidney injury (eGFR < 50mL/min)	**1180/3857 (31%)**	**1119/3748 (30%)**	**61/109 (56%)**	**< 0.001**
Hemodialysis	**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 (< 55mmHg)	996/3857 (26%)	960/3748 (26%)	36/109 (33%)	0.081
Severe pulmonary arterial hypertension (> 55mmHg)	**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 aorto-coronary bypasses **0** **1** **2** **3 and more**	 **1577/3857 (40.8%)** **196/3857 (5.1%)** **812/3857 (21.1%)** **1272/3857 (33%)**	 **1523/3748 (40.6%)** **184/3748 (4.9%)** **788/3748 (21%)** **1253/3748 (33.4%)**	 **54/109 (49.5%)** **12/109 (11%)** **24/109 (22%)** **19/109 (17.4%)**	**< 0.001**
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). Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, COPD = Chronic Obstructive Pulmonary Disease, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction

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

	Unadjusted HR (95% IC)	Multivariable analysis HR (95% IC)	p-value
Time-dependent survival analysis			
Troponin levels (per-1-ng/L increase)	1.01 (1.01 – 1.01)	1.01 (1.01 – 1.02)	< 0.001
Redo surgery	2.95 (2.29 – 3.80)	2.83 (1.35 – 5.94)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	12.19 (5.91 – 25.14)	< 0.001
Creatininemia (per-1-µmol/L increase)	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.03)	< 0.001
Survival analysis (peak troponin & creatinine at baseline)			
Peak troponin (per-1-ng/L increase)	1.01 (1.01 – 1.01)	1.01 (1.00 – 1.01)	< 0.001
Redo surgery	3.25 (1.90 – 5.57)	2.75 (1.05 – 7.24)	< 0.001
Preoperative critical state	7.12 (4.11 – 12.36)	9.69 (4.14 – 22.67)	< 0.001
Creatinine at baseline (per-1-µmol/L increase)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)	< 0.001
10-times upper normal troponin value ($troponin_{10N}$) threshold survival analysis			
Above $troponin_{10N}$ threshold	2.61 (1.48 – 5.13)	1.94 (1.01 – 3.73)	0.047
Redo surgery	2.95 (2.29 – 3.80)	2.68 (1.37 – 5.25)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	7.87 (3.91 – 15.87)	< 0.001
Creatininemia (per-1-µmol/L increase)	1.03 (1.03 – 1.04)	1.03 (1.01 – 1.04)	0.004

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

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

Abbreviations: AKIN: acute kidney injury network

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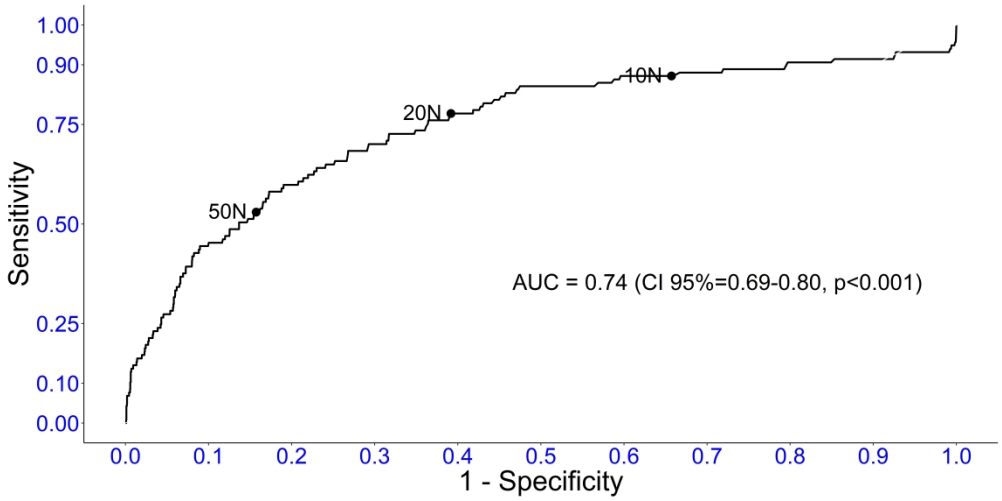

Figure 1. Receiver Operator Characteristics (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality

968x484mm (236 x 236 DPI)

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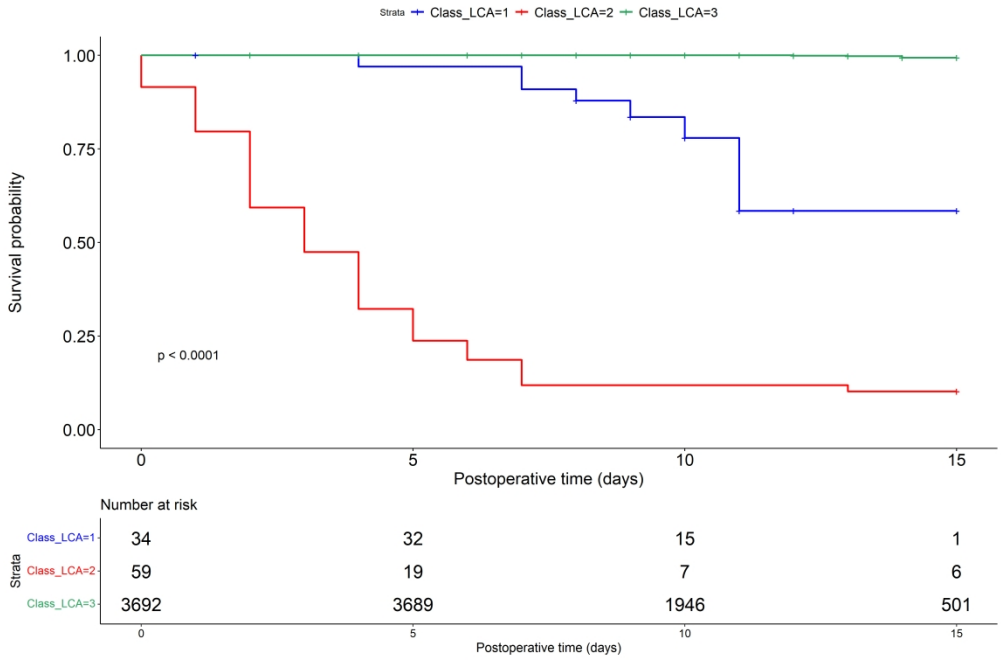

Figure 2. Survival curves depending on latent classes, regarding in-hospital mortality (censored at 15 days). Latent classes (LCA) are categorized as follow: 1: represent stable troponin, 2: represent increasing troponin and 3: represent decreasing troponin trend.

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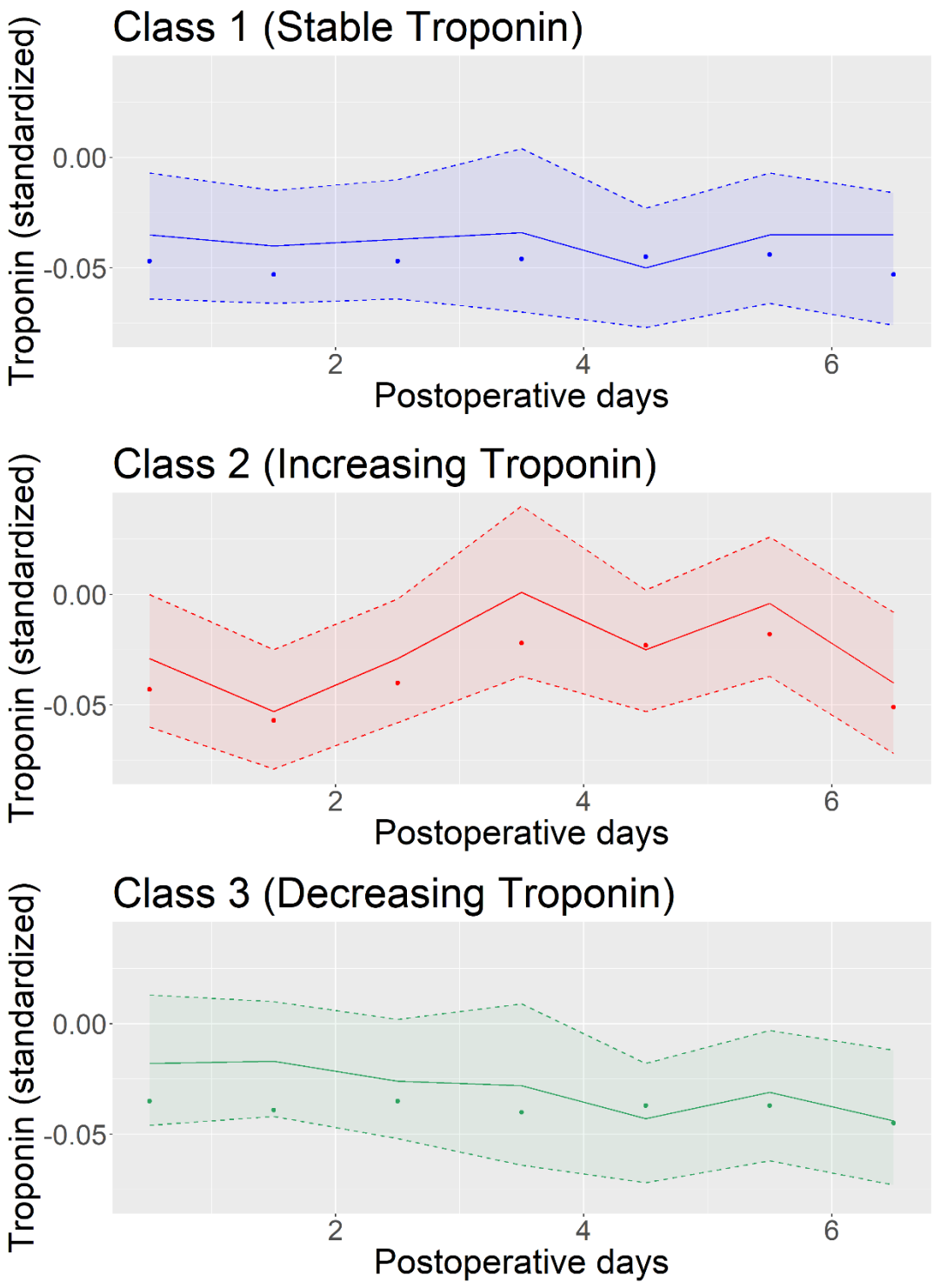
Supplementary Material

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.



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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-unit increase)	1.05	1.02	1.08	< 0.001
C-reactive protein (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Troponin (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Peak troponin (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Creatinine (per-1-unit increase)	1.01	1.01	1.01	< 0.001
Peak creatinine (per-1-unit 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

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

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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
$Troponin_{20N}$ (=3.2 ng/mL)	76.64%	61.09%	5.34%	98.92%
$Troponin_{50N}$ (=8 ng/mL)	52.34%	84.47%	8.81%	98.41%

Supplementary Table 3. Multivariable analysis assessing the association between 20-times normal troponin threshold and in-hospital mortality.

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p
> 20 times upper norm value of troponin	3.74 (2.38 – 5.89)	3.86 (2.23 – 6.69)	< 0.001
Redux	2.95 (2.29 – 3.80)	2.38 (1.22 – 4.64)	0.011
Preoperative critical state	21.20 (13.77 – 32.64)	7.10 (3.53 – 14.25)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.04)	< 0.001

Supplementary Table 4. Multivariable analysis assessing the association between 50-times normal troponin threshold and in-hospital mortality.

	Univariate analysis HR (95% IC)	Multivariate analysis HR (95% IC)	p
> 50 times upper norm value of troponin	4.27 (2.89 – 6.31)	3.74 (2.36 – 5.94)	< 0.001
Redux	2.95 (2.29 – 3.80)	2.45 (1.25 – 4.78)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	6.12 (3.04 – 12.32)	< 0.001
Creatinine	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.04)	< 0.001

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Incidence of troponin elevation and its prognostic value after cardiac surgery

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Keywords:	Cardiac surgery < SURGERY, Adult intensive & critical care < ANAESTHETICS, Adult cardiology < CARDIOLOGY

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Incidence of troponin elevation and its prognostic value after cardiac surgery

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Abstract (233 words)

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, analyzed as time-dependent variable, to predict mortality, independently from other biomarkers; and to assess the incidence and prognosis of a 10-times-upper-norm-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, SGOT, SGPT, 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 was independently associated with mortality after cardiac surgery. This association was independent from inflammatory syndrome, renal and liver failure. $Troponin_{10N}$ was reached in almost all patients, questioning the relevance of this criteria to define postoperative myocardial infarctions after cardiac surgery.

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Article summary - Strengths and limitations of this study

-In this large prospective cohort, troponin was associated with in-hospital mortality, independently from all confounders, including renal function and inflammation.

-Overall, 99.3% of patients presented at least 10-times upper-norm-value troponin elevation, which may correspond to type 5 myocardial infarction, as defined by the fourth universal definition.

-Defining more appropriate thresholds may yield better specificity and trigger specific management such as coronary angiography when reached.

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Introduction

Cardiac surgery procedures have a higher risk of postoperative complications, including death, as compared to 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 cardiac injury. Its polypeptide structure differs from the sequence of skeletal troponins and rises in myocardial hypoxemia. It is routinely used for myocardial infarction diagnosis,[1] even after cardiac surgery.[2] It is also known to yield 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 hospitalized population.[6]

After cardiac surgery, troponin has been associated with reliable prognostic value.[7, 8] Previous studies analyzed troponin as a binary single-timepoint variable (i.e. elevated or not, at a pre-specified 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-norm-value is common to several, including the fourth universal definition of myocardial infarction.

In the present work, we accounted for repeated troponin levels 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

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assess the prognosis 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 analyzed the prognostic value of this threshold.

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Methods

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

Data came from the Registry for the Improvement of Postoperative Outcomes in Cardiac and Thoracic Surgery (RIPOSTE) database, registered at clinicaltrials.gov under NCT03209674. This registry was declared to the Commission nationale de l'informatique et des libertés (CNIL 2109982). The RIPOSTE database recorded prospectively patient's pre-operative and post-operative characteristics. Laboratory data were extracted; they included all in-hospital levels of cardiac troponin, creatinine, lactate, transaminases, bilirubin, 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 EuroSCORE II, laboratory data, and in-hospital mortality. Echocardiographic parameters were prospectively collected in the database. Data were anonymized per national regulations and used with the approval of an institutional review board committee. Data collection was authorized 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

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massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support or preoperative acute renal failure (anuria or oliguria <10 ml/h). Redo surgery was defined as a history of cardiac surgery.

Biomarkers

Troponin. Cardiac I-troponin levels was measured with immunoanalysis ABBOT Architect I2000SR automaton, by CMIA (*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 ABBOT 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-to-1.9-fold increase in creatinine or increase of more than 0.3mg/dL (26.5µmol/L). Stage 2: 2-to-2.9-fold increase from baseline. Stage 3 was defined as an elevation of more than 3 times compared to baseline or an increase to more than 4mg/dL (353.6µmol/L) and acute increase of more than 0.5mg/dL (44.2µmol/L).

Statistical analysis

Categorical variables were expressed as absolute number and percentage. Continuous variables were expressed as median and interquartile range (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, 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 optimize both Akaike information criterion (AIC), measuring the relative goodness-of-fit of the models,[16] and Bayesian information criterion (BIC) which penalizes model

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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 curves and by computing the area under curve (AUROC) with a 95% confidence interval (95%CI).

Additional analyses focused on peak troponin, instead of time-dependent troponin, using Cox regression models. Finally, we performed a latent class analysis 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 optimization of log-likelihood and BIC.

As secondary analyses, we focused on serum creatinine (as a continuous variable), observed as 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 version 4.0.4 (The R Foundation for Statistical Computing).

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Results

Over a 4-year period, we retained 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 CABG in 2280/3857, 59 % patients and isolated valve repair or replacement in 1577/3857, 54 % patients.

In-hospital mortality was 109/3857, 2.8% (variables associated with mortality in unadjusted univariate survival analysis are detailed in **Supplementary 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 norm 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 hazard-ratio (adj.HR)=1.01 (CI95%=1.01-1.01, p<0.001) in a multivariable model adjusting for time-dependent creatinine, Redo surgery, and preoperative critical state (see **Table 2a**).

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

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peak troponin and mortality (per 1 ng/mL increase, adju.HR=1.01 (CI 95%=1.01-1.01, p<0.001)(see **Table 2b**).

A receiver operating characteristics (ROC) curve was drawn to assess discrimination feature of peak troponin, regarding in-hospital postoperative mortality (see **Figure 1**). Its area under the curve (AUC) was 0.74 (CI95%=0.69-0.80, p<0.001). Remarkably, a peak troponin higher than 100 times upper norm value (labeled $troponin_{100N}$ 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 (CI 95%=1.48-1.84, p < 0.001), confirmed in multivariable analysis after adjusting for creatinine, preoperative critical state, and redo surgery (adj.HR=2.31 (CI95%=2.01-2.66, p<0.001)(see **Table 2c**). 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 (CI95%=1.33 – 1.60) and 1.68 (1.52 – 1.86)), confirmed in multivariable analysis (respective adj. HR 1.75 (CI95%=1.57 – 1.94) and 1.57 (1.41 – 1.75)). Details on models, sensitivity, specificity and predictive values, are presented in **Supplementary Tables 2, 3 and 4**.

In a secondary analysis, we performed latent class analysis which accounted for variations of troponin over time, assessing three paths with independent classes (see **Supplementary 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 to patients with stable (0.91 % of patients) or decreasing troponin (96.9% of patients). Increasing troponin class was

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significantly associated with in-hospital mortality compared to the two other classes (HR 11.6, CI95% 7.22-18.80).

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-µmol/L-increase adj.HR=1.02 (CI 95%=1.01-1.02, p < 0.001)(see **Table 3a**). When considering AKI severity, mortality was increased for each class increase in AKIN/KDIGO (adj.HR=2.83 (CI95%=2.63-3.03, p < 0.001) (see **Table 3b**).

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 (CI95%=1.01-1.01) and 1.05 (CI95%=1.02-1.08), p<0.001 for both. However, these biomarkers were not independently associated with mortality, once accounting for troponin and serum creatinine. Meanwhile, SGOT and SGPT were not associated with in-hospital mortality.

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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 time-dependent survival analyses adjusting for several cofounding factors.

The main findings of our study are: i) all patients develop a peak troponin after cardiac surgery above normal, and 99.3% above 10 times the upper norm value; ii) troponin, whether assessed as a single value, or as a time-dependent variable, was associated with in-hospital mortality; iii) this association remained significant after accounting for confounders which included renal function, inflammation, and liver function; and iii) 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 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 complications,[22] 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 CK definition. The injury threshold changed over time and studies such as the one we present. The ESC Joint WGs position paper,[2] used several threshold 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

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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 post-operative complication. Acute CABG occlusion or coronary ischemia 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 exam 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 analyzing 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 prognostic value of troponin rise, reflecting cardiomyocytes 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 shown [25] in a monocentric cohort of patients with valvular disease. A meta-analysis gathering 17 studies concluded in a strong correlation between post-operative troponin elevation and mortality in a CABG and valvular population (OR 5.46 for 30-days 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 Ventricle Ejection Fraction (LVEF), elevated NYHA, 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,

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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, ischemia/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 anemia 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 (ASAT/ALAT 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.

Independently from 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], RIFLE or AKIN criteria [28-30]. Even minimal changes in creatinine as small as 0.5 mg/dL was found to be associated with 30-days mortality [31]. However, similarly 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 to 4 times in previous studies for an elevation of 0.5mg/dL [31]) 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 to 5.5 and 8.4, respectively).[31]

The present study strengths include a longitudinal troponin measurement allowing a better evaluation of rise/fall, believed to be a better reflect of myocardial injury, a high number of inclusions, a homogeneous population with a systematic biological follow-up. We acknowledge several limitations to our study. A single centered cohort has a limited external validation, though the population's characteristics appear to be representative of a standard cardiac surgery patient. Main

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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. In a recent work published by Devereaux et al. showed that the threshold associated with mortality requiring to be at least 218 times the upper-norm-value on the first day after surgery to be significantly associated with mortality.[36] 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 multicenter prospective initiative with systematic coronary angiography may adequately answer this question.

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Conclusion

In this cohort study, postoperative troponin was significantly associated with in-hospital mortality, whether analyzed as a time-dependent (i.e. 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 upper norm value, questioning the relevance of this threshold to define postoperative myocardial infarctions after cardiac surgery.

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Contributorship statement. A. Clement wrote the manuscript, A. Daulasim performed analyses, M. Souibri participated to data collection and provided critical review to the manuscript and L.S. Nguyen cowrote the manuscript and supervised this study.

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Competing interests: none

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

Ethics Approval. This study was approved by an Ethics committee and declared to the French relevant organism, Commission nationale de l'informatique et des libertés (CNIL 2109982).

Data sharing statement. Data may be shared upon reasonable request.

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Figures legend and Tables

Figure 1. Receiver Operator Characteristics (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality

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

Table 1. Clinical and biological characteristics

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

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

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 mortality in unadjusted univariate survival analysis

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

Supplementary Table 3. Multivariable analysis assessing the association between 20-times normal troponin threshold and in-hospital mortality.

Supplementary Table 4. Multivariable analysis assessing the association between 50-times normal troponin threshold and in-hospital mortality.

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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, u/L	**22 (17 – 30)**	**22 (17 – 30)**	**30 (19 – 46)**	**< 0.001**
ALT, u/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**
Pre-operative 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**
Post-infarction 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
Dyspnea **NYHA 2** **NYHA 3** **NYHA 4**	 **619 (16%)** **711 (18%)** **51 (1.3%)**	 **608 (16%)** **680 (18%)** **37 (1%)**	 **11 (10%)** **31 (28%)** **14 (13%)**	**< 0.001**
Active endocarditis	**110/3857 (2.9%)**	**98/3748 (2.6%)**	**12/109 (11%)**	**< 0.001**

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Number of associated non-CABG procedures **1** **2** **3**	 **1212 (31%)** **682 (18%)** **57 (1.5%)**	 **1174 (31%)** **649 (17%)** **52 (1.4%)**	 **38 (35%)** **33 (30%)** **5 (4.6%)**	**0.03**
Moderate kidney injury (eGFR 50 – 85mL/min)	**1973/3857 (51%)**	**1937/3748 (52%)**	**36/109 (33%)**	**< 0.001**
Severe kidney injury (eGFR < 50mL/min)	**1180/3857 (31%)**	**1119/3748 (30%)**	**61/109 (56%)**	**< 0.001**
Hemodialysis	**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 (< 55mmHg)	996/3857 (26%)	960/3748 (26%)	36/109 (33%)	0.081
Severe pulmonary arterial hypertension (> 55mmHg)	**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 aorto-coronary bypasses **0** **1** **2** **3 and more**	 **1577/3857 (40.8%)** **196/3857 (5.1%)** **812/3857 (21.1%)** **1272/3857 (33%)**	 **1523/3748 (40.6%)** **184/3748 (4.9%)** **788/3748 (21%)** **1253/3748 (33.4%)**	 **54/109 (49.5%)** **12/109 (11%)** **24/109 (22%)** **19/109 (17.4%)**	**< 0.001**
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). Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, COPD = Chronic Obstructive Pulmonary Disease, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction

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

	Unadjusted HR (95% IC)	Multivariable analysis HR (95% IC)	p-value
Time-dependent survival analysis			
Troponin levels (per-1-ng/mL increase)	1.01 (1.01 – 1.01)	1.01 (1.01 – 1.02)	< 0.001
Redo surgery	2.95 (2.29 – 3.80)	2.83 (1.35 – 5.94)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	12.19 (5.91 – 25.14)	< 0.001
Creatininemia (per-1-µmol/L increase)	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.03)	< 0.001
Survival analysis (peak troponin & creatinine at baseline)			
Peak troponin (per-1-ng/mL increase)	1.01 (1.01 – 1.01)	1.01 (1.00 – 1.01)	< 0.001
Redo surgery	3.25 (1.90 – 5.57)	2.75 (1.05 – 7.24)	< 0.001
Preoperative critical state	7.12 (4.11 – 12.36)	9.69 (4.14 – 22.67)	< 0.001
Creatinine at baseline (per-1-µmol/L increase)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)	< 0.001
100-times upper normal troponin value ($troponin_{10N}$) threshold survival analysis			
Above $troponin_{100N}$ threshold	1.65 (1.48 – 1.84)	2.31 (2.01 – 2.66)	< 0.001
Redo surgery	2.95 (2.29 – 3.80)	2.91 (2.45 – 3.45)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	11.19 (9.42 – 13.30)	< 0.001
Creatininemia (per-1-µmol/L increase)	1.03 (1.03 – 1.04)	1.02 (1.02 – 1.03)	< 0.001

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

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

Abbreviations: AKIN: acute kidney injury network

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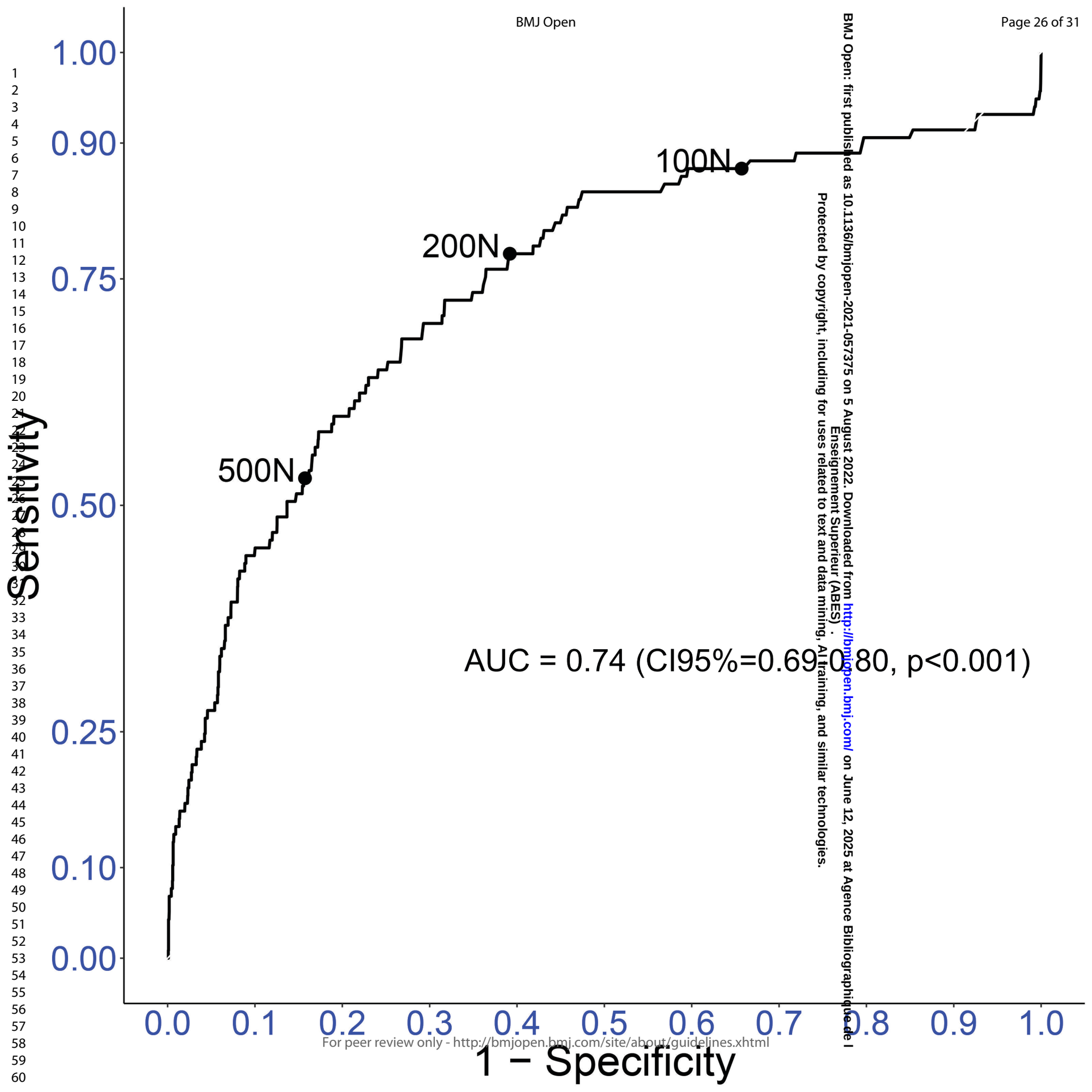

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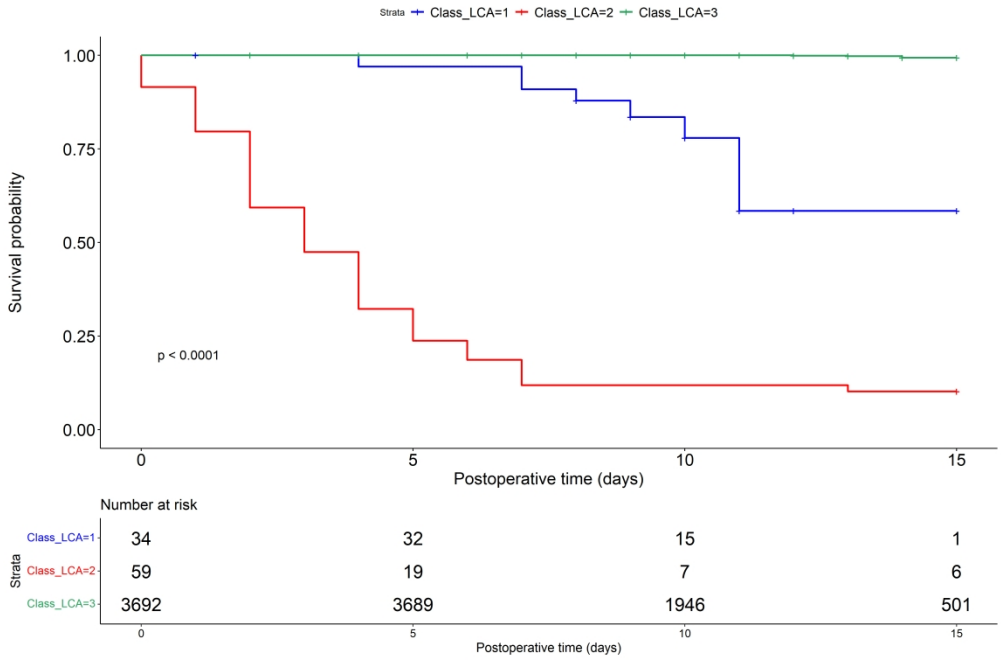

Figure 2. Survival curves depending on latent classes, regarding in-hospital mortality (censored at 15 days). Latent classes (LCA) are categorized as follow: 1: represent stable troponin, 2: represent increasing troponin and 3: represent decreasing troponin trend.

968x645mm (118 x 118 DPI)

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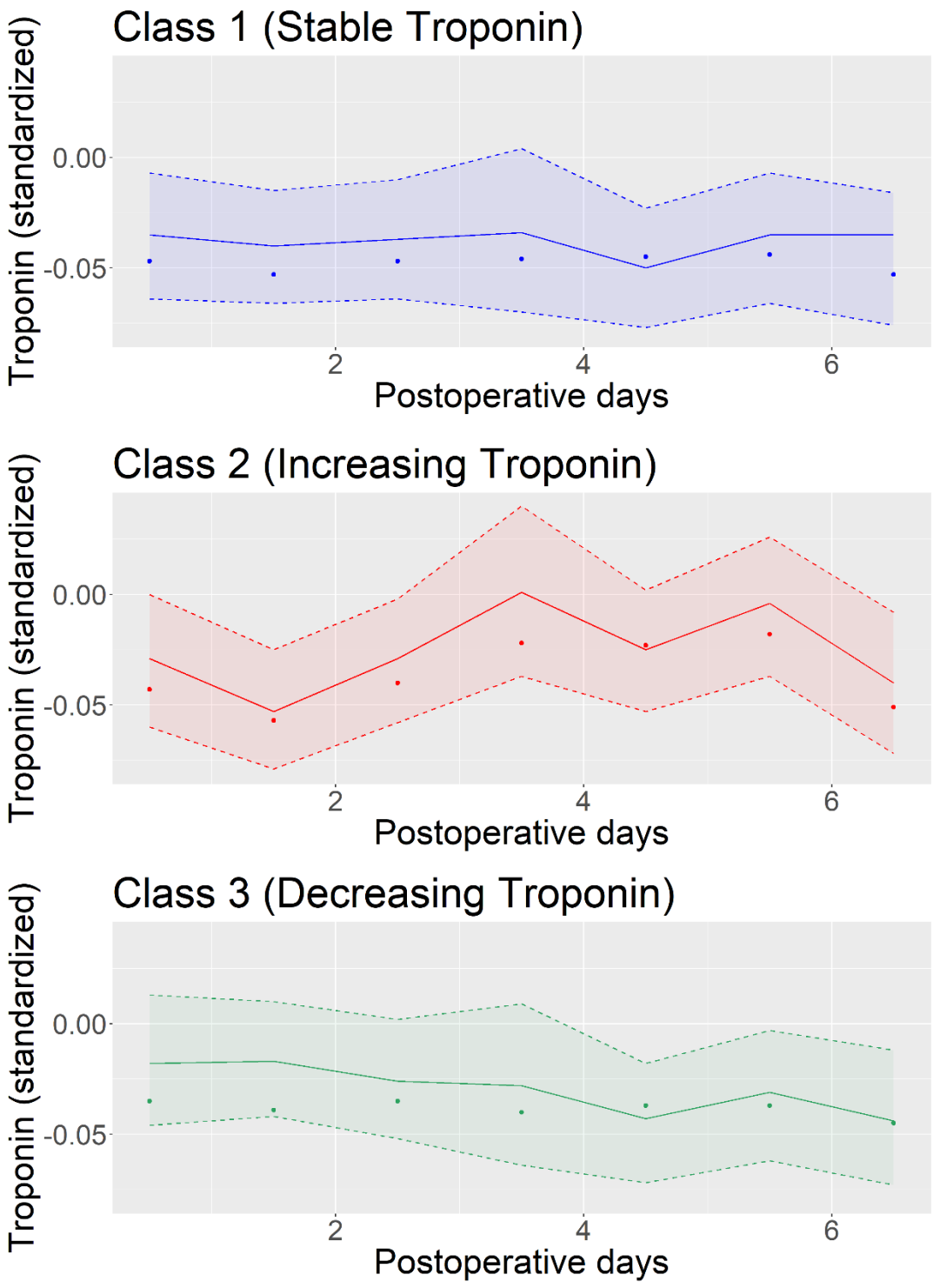
Supplementary Material

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.



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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- µmol/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- µmol/L increase)	1.01	1.01	1.01	< 0.001
Peak creatinine (per-1- µmol/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

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

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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

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Cardiac surgery < SURGERY, Adult intensive & critical care < ANAESTHETICS, Adult cardiology < CARDIOLOGY

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

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Abstract (234 words)

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, analyzed as time-dependent variable, to predict mortality, independently from other biomarkers; and to assess the incidence and prognosis of a 10-times-upper-norm-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, SGOT, SGPT, 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 from inflammatory syndrome, renal and liver failure. $Troponin_{10N}$ was reached in almost all patients, questioning the relevance of this criteria to define postoperative myocardial infarctions after cardiac surgery.

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Strengths and limitations of this study

-In this large single-center prospective cohort study, all consecutive patients who underwent cardiac surgery with cardiopulmonary bypass were included, over a four-year period.

-Biomarkers including troponin levels were routinely assessed around in 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 effect models, and discrimination evaluation.

-Confounding variables such as EuroSCORE 2 and procedure type were accounted for.

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Introduction

Cardiac surgery procedures have a higher risk of postoperative complications, including death, as compared to 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 cardiac injury. Its polypeptide structure differs from the sequence of skeletal troponins and rises in myocardial hypoxemia. It is routinely used for myocardial infarction diagnosis,[1] even after cardiac surgery.[2] It is also known to yield 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 hospitalized population.[6]

After cardiac surgery, troponin has been associated with reliable prognostic value.[7, 8] Previous studies analyzed troponin as a binary single-timepoint variable (i.e. elevated or not, at a pre-specified 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-norm-value is common to several, including the fourth universal definition of myocardial infarction.

In the present work, we accounted for repeated troponin levels 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

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assess the prognosis 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 analyzed the prognostic value of this threshold.

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Methods

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

Data came from the Registry for the Improvement of Postoperative Outcomes in Cardiac and Thoracic Surgery (RIPOSTE) database, registered at clinicaltrials.gov under NCT03209674. This registry was declared to the Commission nationale de l'informatique et des libertés (CNIL 2109982). The RIPOSTE database recorded prospectively patient's pre-operative and post-operative characteristics. Laboratory data were extracted; they included all in-hospital levels of cardiac troponin, creatinine, lactate, transaminases, bilirubin, 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 EuroSCORE II, laboratory data, and in-hospital mortality. Echocardiographic parameters were prospectively collected in the database. Data were anonymized per national regulations and used with the approval of an institutional review board committee. Data collection was authorized 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

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massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support or preoperative acute renal failure (anuria or oliguria <10 ml/h). Redo surgery was defined as a history of cardiac surgery.

Biomarkers

Troponin. Cardiac I-troponin levels was measured with immunoanalysis ABBOT Architect I2000SR automaton, by CMIA (*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 ABBOT 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-to-1.9-fold increase in creatinine or increase of more than 0.3mg/dL (26.5µmol/L). Stage 2: 2-to-2.9-fold increase from baseline. Stage 3 was defined as an elevation of more than 3 times compared to baseline or an increase to more than 4mg/dL (353.6µmol/L) and acute increase of more than 0.5mg/dL (44.2µmol/L).

Statistical analysis

Categorical variables were expressed as absolute number and percentage. Continuous variables were expressed as median and interquartile range (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, 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 optimize both Akaike information criterion (AIC), measuring the relative goodness-of-fit of the models,[16] and Bayesian information criterion (BIC) which penalizes model

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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 curves and by computing the area under curve (AUROC) with a 95% confidence interval (95%CI).

Additional analyses focused on peak troponin, instead of time-dependent troponin, using Cox regression models. Finally, we performed a latent class analysis 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 optimization of log-likelihood and BIC.

As secondary analyses, we focused on serum creatinine (as a continuous variable), observed as 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 version 4.0.4 (The R Foundation for Statistical Computing).

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

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Results

Over a 4-year period, we retained 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 CABG in 2280/3857, 59 % patients and isolated valve repair or replacement in 1577/3857, 54 % patients.

In-hospital mortality was 109/3857, 2.8% (variables associated with mortality in unadjusted univariate survival analysis are detailed in **Supplementary 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 norm 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 hazard-ratio (adj.HR)=1.01 (CI95%=1.01-1.01, p<0.001) in a multivariable model adjusting for time-dependent creatinine, Redo surgery, and preoperative critical state (see **Table 2a**).

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

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peak troponin and mortality (per 1 ng/mL increase, adju.HR=1.01 (CI 95%=1.01-1.01, p<0.001)(see **Table 2b**).

A receiver operating characteristics (ROC) curve was drawn to assess discrimination feature of peak troponin, regarding in-hospital postoperative mortality (see **Figure 1**). Its area under the curve (AUC) was 0.74 (CI95%=0.69-0.80, p<0.001). Remarkably, a peak troponin higher than 100 times upper norm value (labeled $troponin_{100N}$ 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 (CI 95%=1.48-1.84, p < 0.001), confirmed in multivariable analysis after adjusting for creatinine, preoperative critical state, and redo surgery (adj.HR=2.31 (CI95%=2.01-2.66, p<0.001)(see **Table 2c**). 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 (CI95%=1.33 – 1.60) and 1.68 (1.52 – 1.86)), confirmed in multivariable analysis (respective adj. HR 1.75 (CI95%=1.57 – 1.94) and 1.57 (1.41 – 1.75)). Details on models, sensitivity, specificity and predictive values, are presented in **Supplementary Tables 2, 3 and 4**.

In a secondary analysis, we performed latent class analysis which accounted for variations of troponin over time, assessing three paths with independent classes (see **Supplementary 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 to patients with stable (0.91 % of patients) or decreasing troponin (96.9% of patients). Increasing troponin class was

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significantly associated with in-hospital mortality compared to the two other classes (HR 11.6, CI95% 7.22-18.80).

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-µmol/L-increase adj.HR=1.02 (CI 95%=1.01-1.02, p < 0.001)(see **Table 3a**). When considering AKI severity, mortality was increased for each class increase in AKIN/KDIGO (adj.HR=2.83 (CI95%=2.63-3.03, p < 0.001) (see **Table 3b**).

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 (CI95%=1.01-1.01) and 1.05 (CI95%=1.02-1.08), p<0.001 for both. However, these biomarkers were not independently associated with mortality, once accounting for troponin and serum creatinine. Meanwhile, SGOT and SGPT were not associated with in-hospital mortality.

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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 time-dependent survival analyses adjusting for several cofounding factors.

The main findings of our study are: i) all patients develop a peak troponin after cardiac surgery above normal, and 99.3% above 10 times the upper norm value; ii) troponin, whether assessed as a single value, or as a time-dependent variable, was associated with in-hospital mortality; iii) this association remained significant after accounting for confounders which included renal function, inflammation, and liver function; and iii) 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 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 complications,[22] 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 CK definition. The injury threshold changed over time and studies such as the one we present. The ESC Joint WGs position paper,[2] used several threshold 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

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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 post-operative complication. Acute CABG occlusion or coronary ischemia 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 exam 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 analyzing 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 prognostic value of troponin rise, reflecting cardiomyocytes 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 shown [25] in a monocentric cohort of patients with valvular disease. A meta-analysis gathering 17 studies concluded in a strong correlation between post-operative troponin elevation and mortality in a CABG and valvular population (OR 5.46 for 30-days 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 Ventricle Ejection Fraction (LVEF), elevated NYHA, 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,

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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, ischemia/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 anemia 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 (ASAT/ALAT 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.

Independently from 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], RIFLE or AKIN criteria [28-30]. Even minimal changes in creatinine as small as 0.5 mg/dL was found to be associated with 30-days mortality [31]. However, similarly 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 to 4 times in previous studies for an elevation of 0.5mg/dL [31]) 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 to 5.5 and 8.4, respectively).[31]

The present study strengths include a longitudinal troponin measurement allowing a better evaluation of rise/fall, believed to be a better reflect of myocardial injury, a high number of inclusions, a homogeneous population with a systematic biological follow-up. We acknowledge several limitations to our study. A single centered cohort has a limited external validation, though the population's characteristics appear to be representative of a standard cardiac surgery patient. Main

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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. In a recent work published by Devereaux et al. showed that the threshold associated with mortality requiring to be at least 218 times the upper-norm-value on the first day after surgery to be significantly associated with mortality.[36] 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 multicenter prospective initiative with systematic coronary angiography may adequately answer this question.

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Conclusion

In this cohort study, postoperative troponin was significantly associated with in-hospital mortality, whether analyzed as a time-dependent (i.e. 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 upper norm value, questioning the relevance of this threshold to define postoperative myocardial infarctions after cardiac surgery.

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Figures legend and Tables

Figure 1. Receiver Operator Characteristics (ROC) curve of troponin peak after cardiac surgery, regarding in-hospital mortality

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

Table 1. Clinical and biological characteristics

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

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

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 mortality in unadjusted univariate survival analysis

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

Supplementary Table 3. Multivariable analysis assessing the association between 20-times normal troponin threshold and in-hospital mortality.

Supplementary Table 4. Multivariable analysis assessing the association between 50-times normal troponin threshold and in-hospital mortality.

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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, u/L	**22 (17 – 30)**	**22 (17 – 30)**	**30 (19 – 46)**	**< 0.001**
ALT, u/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**
Pre-operative 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**
Post-infarction 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
Dyspnea **NYHA 2** **NYHA 3** **NYHA 4**	 **619 (16%)** **711 (18%)** **51 (1.3%)**	 **608 (16%)** **680 (18%)** **37 (1%)**	 **11 (10%)** **31 (28%)** **14 (13%)**	**< 0.001**
Active endocarditis	**110/3857 (2.9%)**	**98/3748 (2.6%)**	**12/109 (11%)**	**< 0.001**

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Number of associated non-CABG procedures **1** **2** **3**	 **1212 (31%)** **682 (18%)** **57 (1.5%)**	 **1174 (31%)** **649 (17%)** **52 (1.4%)**	 **38 (35%)** **33 (30%)** **5 (4.6%)**	**0.03**
Moderate kidney injury (eGFR 50 – 85mL/min)	**1973/3857 (51%)**	**1937/3748 (52%)**	**36/109 (33%)**	**< 0.001**
Severe kidney injury (eGFR < 50mL/min)	**1180/3857 (31%)**	**1119/3748 (30%)**	**61/109 (56%)**	**< 0.001**
Hemodialysis	**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 (< 55mmHg)	996/3857 (26%)	960/3748 (26%)	36/109 (33%)	0.081
Severe pulmonary arterial hypertension (> 55mmHg)	**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 aorto-coronary bypasses **0** **1** **2** **3 and more**	 **1577/3857 (40.8%)** **196/3857 (5.1%)** **812/3857 (21.1%)** **1272/3857 (33%)**	 **1523/3748 (40.6%)** **184/3748 (4.9%)** **788/3748 (21%)** **1253/3748 (33.4%)**	 **54/109 (49.5%)** **12/109 (11%)** **24/109 (22%)** **19/109 (17.4%)**	**< 0.001**
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). Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, COPD = Chronic Obstructive Pulmonary Disease, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction

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

	Unadjusted HR (95% IC)	Multivariable analysis HR (95% IC)	p-value
Time-dependent survival analysis			
Troponin levels (per-1-ng/mL increase)	1.01 (1.01 – 1.01)	1.01 (1.01 – 1.02)	< 0.001
Redo surgery	2.95 (2.29 – 3.80)	2.83 (1.35 – 5.94)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	12.19 (5.91 – 25.14)	< 0.001
Creatininemia (per-1-µmol/L increase)	1.03 (1.03 – 1.04)	1.02 (1.01 – 1.03)	< 0.001
Survival analysis (peak troponin & creatinine at baseline)			
Peak troponin (per-1-ng/mL increase)	1.01 (1.01 – 1.01)	1.01 (1.00 – 1.01)	< 0.001
Redo surgery	3.25 (1.90 – 5.57)	2.75 (1.05 – 7.24)	< 0.001
Preoperative critical state	7.12 (4.11 – 12.36)	9.69 (4.14 – 22.67)	< 0.001
Creatinine at baseline (per-1-µmol/L increase)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)	< 0.001
100-times upper normal troponin value ($troponin_{10N}$) threshold survival analysis			
Above $troponin_{100N}$ threshold	1.65 (1.48 – 1.84)	2.31 (2.01 – 2.66)	< 0.001
Redo surgery	2.95 (2.29 – 3.80)	2.91 (2.45 – 3.45)	< 0.001
Preoperative critical state	21.20 (13.77 – 32.64)	11.19 (9.42 – 13.30)	< 0.001
Creatininemia (per-1-µmol/L increase)	1.03 (1.03 – 1.04)	1.02 (1.02 – 1.03)	< 0.001

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

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

Abbreviations: AKIN: acute kidney injury network

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Statements

a. **Contributorship.** A. Clement wrote the manuscript, A. Daulasim performed analyses, M. Souibri participated to data collection and provided critical review to the manuscript and L.S. Nguyen cowrote the manuscript and supervised this study

b. **Funding.** None

c. **Competing of Interests.** None

d. **Ethics Approval.** This study was approved by an Ethics committee and declared to the French relevant organism, Commission nationale de l'informatique et des libertés (CNIL 2109982).

e. **Data sharing.** Data may be shared upon reasonable request. Data are subject to the French national legislation which requires to participating centers to adhere to its laws. Data may be exchanged after submitting adequate forms to the CNIL (Commission Nationale Informatique et Libertés).

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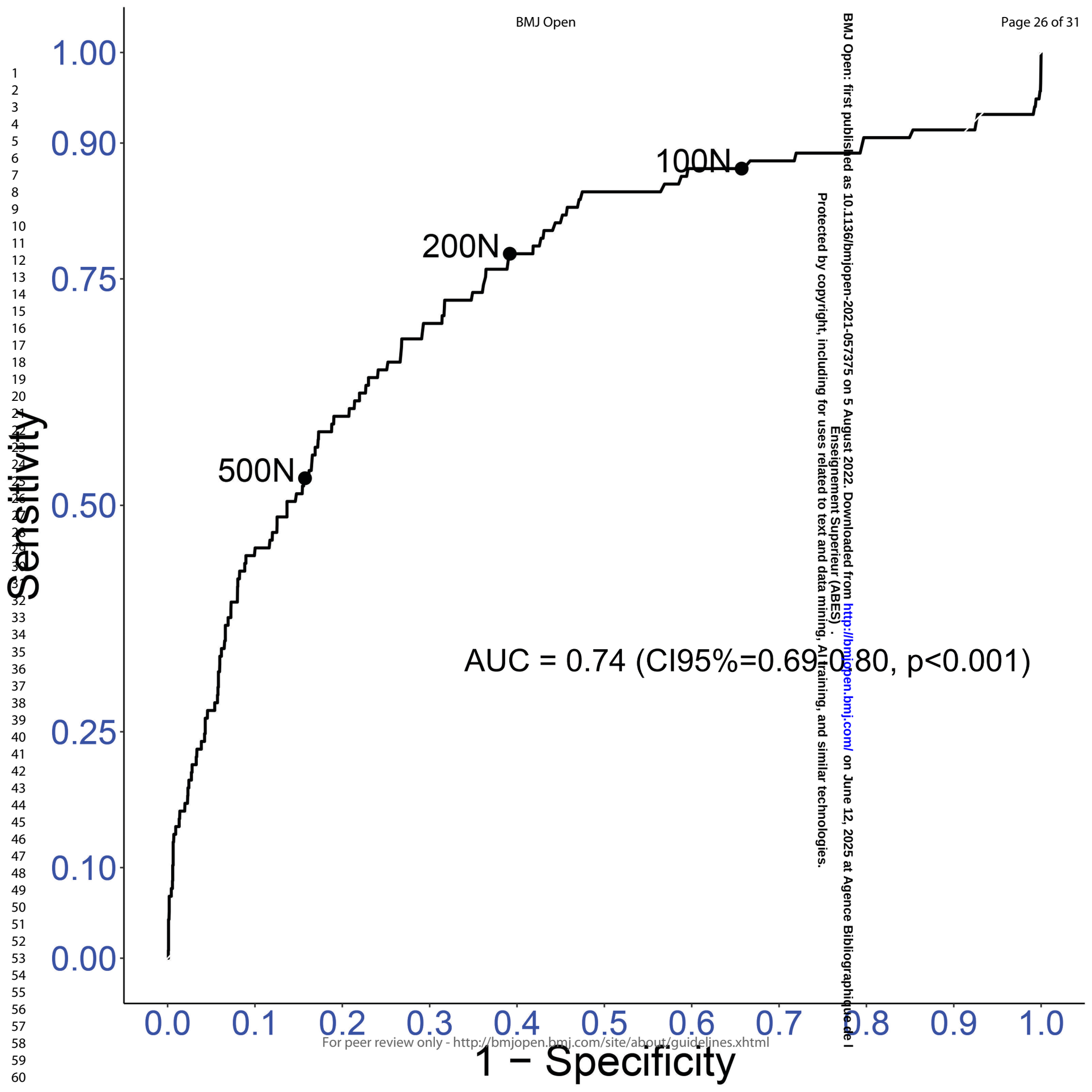

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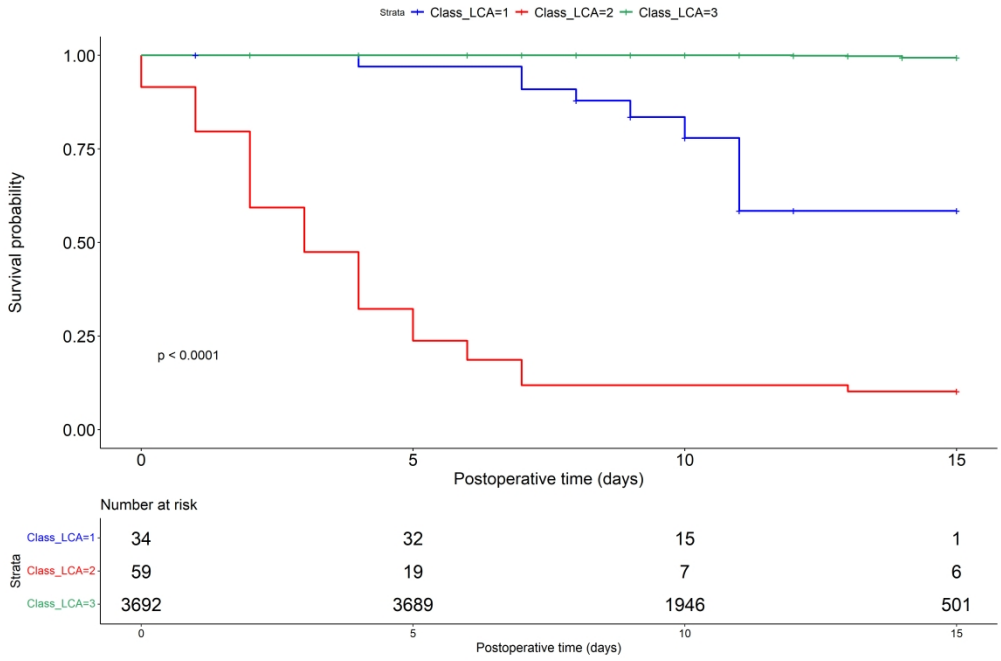

Figure 2. Survival curves depending on latent classes, regarding in-hospital mortality (censored at 15 days). Latent classes (LCA) are categorized as follow: 1: represent stable troponin, 2: represent increasing troponin and 3: represent decreasing troponin trend.

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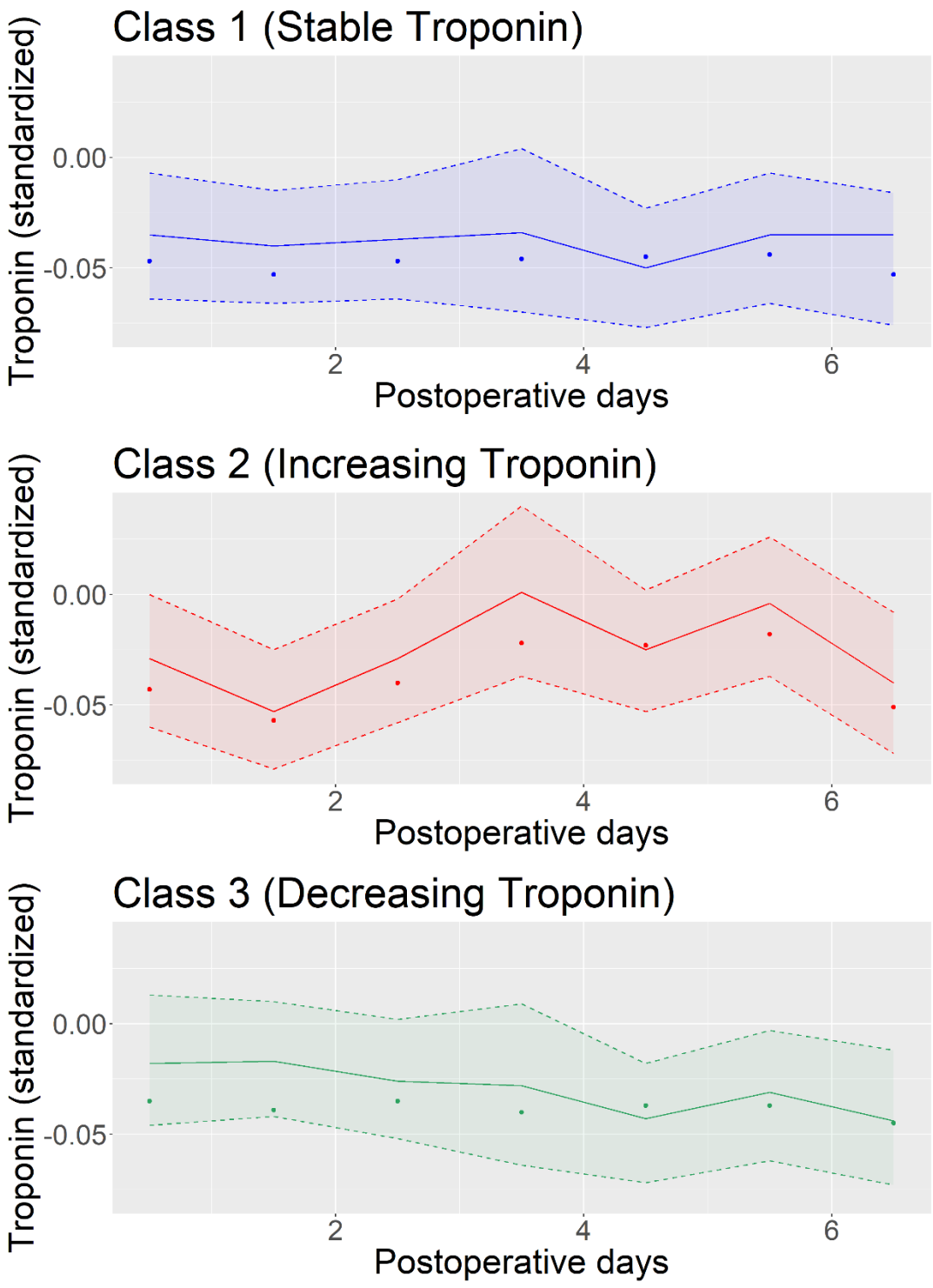
Supplementary Material

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.



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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- µmol/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- µmol/L increase)	1.01	1.01	1.01	< 0.001
Peak creatinine (per-1- µmol/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

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

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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

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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