

ORIGINAL RESEARCH

Prediction of Death After Noncardiac Surgery: Potential Advantage of Using High-Sensitivity Troponin T as a Continuous Variable

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BACKGROUND: Increased high-sensitivity cardiac troponin T (hs-cTnT) above the upper reference limit (URL) after noncardiac surgery identifies patients at risk for mortality. Prior studies have not analyzed hs-cTnT as a continuous variable or probed age- and sex-specific URLs. This study compared the prediction of 30-day mortality using continuous postoperative hs-cTnT levels to the use of the overall URL and age- and sex-specific URLs.

METHODS AND RESULTS: Patients (876) >40 years of age who underwent noncardiac surgery were included. Hs-cTnT was measured on postoperative day 1. Cox proportional hazards models were used to compare associations between 30-day mortality and using hs-cTnT as a continuous variable, or above the overall or age- and sex-specific URLs. Comparisons were performed by the area under the receiver operating characteristic curve analysis. Mortality was 4.2%. For each 1 ng/L increase in postoperative hs-cTnT, there was a 0.3% increase in mortality ($P<0.001$). Patients with postoperative hs-cTnT >14 ng/L were 37% of the cohort, while those above age- and sex-specific URLs were 25.3%. Both manifested higher mortality (hazard ratio [HR], 3.19; 95% CI, 1.20–8.49; $P=0.020$) and (HR, 2.76; $P=0.009$) than those with normal levels. The area under receiver operating characteristic curve was 0.89 using hs-cTnT as a continuous variable, 0.87 for age- and sex-specific URLs, and 0.86 for the overall URL.

CONCLUSIONS: Hs-cTnT as a continuous variable was independently associated with 30-day mortality and had the highest accuracy. Hs-cTnT elevations using overall and/or age- and sex-specific URLs were also associated with higher mortality.

Key Words: noncardiac surgery ■ prognosis ■ troponin

Worldwide, more than 200 million adults undergo noncardiac surgery annually.¹ At least half are >45 years of age, and thus many have comorbidities. The expected early mortality ranges from 1.2% to 6.9%.² Many patients manifest myocardial injury after noncardiac surgery,^{3–5} which represents a spectrum from myocardial infarction (MI) to isolated cardiac troponin elevations above the 99th percentile of the upper reference limit (URL) without clinical or

ECG criteria for MI.⁶ These elevations have been referred to by some as isolated myocardial injury.⁷ Many of them may not meet the universal definition of MI criteria.⁶ However, any elevated cardiac troponin value is a predictor of mortality within the first year after surgery with both standard⁸ and high-sensitivity assays,^{9–15} although the latter detect more elevations.

Data suggest a significant association between peak high-sensitivity cardiac troponin T (hs-cTnT)

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CLINICAL PERSPECTIVE

What Is New?

- There is a continuous relationship between increased values of high-sensitivity cardiac troponin T in the postoperative setting and the risk for cardiovascular events.
- Many of these events are thought to be attributable to type 2 myocardial infarctions, which might be amenable to prevention.

What Are the Clinical Implications?

- Detecting these signals may provide an ability in the long term to identify and treat or even prevent such events.
- For now, physicians can use high-sensitivity cardiac troponin T values to establish threshold values in this setting as reported in the manuscript or simply use continuous data along with clinical judgment to guide patient management.

Nonstandard Abbreviations and Acronyms

| | |
|---------------|--|
| MANAGE | Management of Myocardial Injury After Noncardiac Surgery Trial |
| URL | upper reference limit |
| VISION | Vascular Events in Noncardiac Surgery Patients Cohort Evaluation |

values and 30-day mortality irrespective of the presence or absence of ischemic features.¹⁴ The primary aim of this study was to evaluate the prognostic association of the first postoperative hs-cTnT level (as a continuous variable) after noncardiac surgery and 30-day mortality. We also compared that approach to the use of an overall cutoff value and to sex- and age-specific 99th percentile URLs.

METHODS

Patient Selection

This single-center study evaluated 876 consecutive patients ≥ 40 years of age with 24-hour postoperative hs-cTnT measurement after noncardiac surgery at the Hospital de Base, Faculdade de Medicina de São José do Rio Preto, São Paulo, Brazil. The study population was classified into vascular, gastrointestinal, neurologic, orthopedic, gynecologic/urologic, and thoracic surgery populations. Demographic, laboratory, preoperative, perioperative, and postoperative data were collected from all patients who underwent surgery under general or regional anesthesia at our institution from September 2015 to April 2017. Clinical data were

obtained from the prospective noncardiac surgery database of the Brazilian Biomarker Group. Vital status reports were obtained after discharge from the electronic medical record or by telephone contact made by investigators blinded to the hs-cTnT measurement values. There was no loss of follow-up.

This study was conducted following the Declaration of Helsinki and was approved through the local Human Research Ethics Committee of the Faculdade de Medicina de São José do Rio Preto (CAAE—44670215.2.0000.5415). The need for individual informed consent was waived, as this study was an observational analysis of prospectively collected data for routine clinical care. Breaches of privacy or loss of patient anonymity did not occur.

Troponin Measurements

Hs-cTnT) was measured with the fifth-generation Elecsys Troponin T STAT assay (Roche, Basel, Switzerland). HscTnT was analyzed as a continuous variable (ng/L) after logarithmic transformation as well as a dichotomous variable. Levels above the overall 99th percentile of URL (>14 ng/L) were considered elevated.^{6,16,17} As proposed by Gore et al,¹⁸ age- and sex-specific cutoff levels for hs-cTnT (>17 ng/L for men 50 to 64 years of age and women ≥ 65 years of age, and >31 ng/L for men ≥ 65 years of age) were also evaluated.

All patients had a venous blood sample collected on the morning of the first postoperative day. Because of a lack of a prespecified protocol at that time, only a small subgroup ($n=116$) of nonconsecutive patients also had a preoperative hs-cTnT measurement immediately before surgery, at the discretion of the surgeon or anesthesiologist. In these patients with an additional preoperative hs-cTnT measurement, a rising pattern (Δ hs-cTnT) was considered to be an absolute increase of >7 ng/L above the 99th percentile if the first value was ≤ 14 ng/L to align with reports from others and the European Society of Cardiology guidance.^{6,19,20} If the first value was >14 ng/L, an increase >7 ng/L of the first measurement was considered as a significant Δ change.^{6,19,20}

Statistical Analysis

The data from this study may be available from Dr Machado upon reasonable request.

Variables are presented as absolute numbers and percentages and median and interquartile ranges (25th and 75th percentile). Because of a lack of Gaussian distribution, continuous variables were compared using the nonparametric Mann-Whitney test. Chi-square or Fisher's exact tests were used to compare categorical variables. Additional analyses using log-transformed hs-cTnT data were also performed.

Univariate and multivariable Cox proportional hazards models (stepwise backward elimination method) were used to determine the association between the hs-cTnT as a continuous variable and all-cause 30-day mortality. After the univariate analysis, variables with a $P < 0.15$ and those thought to be of clinical relevance were included in the multivariable model. The hazard ratio (HR) and 95% CIs were calculated for the predictors, and discrimination was assessed through C statistical analysis.

In the univariate Cox regression analysis, age 40 to 64; 65 to 74, and ≥ 75 years, sex (reference: male), ethnicity (reference: African descent), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), heart rate > 100 beats per minute, cardiovascular disease (MI, peripheral arterial disease, transient ischemic attack, and/or cerebrovascular accident), high blood pressure, diabetes mellitus, chronic obstructive pulmonary disease, surgical time (minutes), type of surgery, serum creatinine (mg/dL), estimated glomerular filtration rate calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation,²¹ American Society of Anesthesiologists physical status classification system²² class > 2 , and the first postoperative hs-cTnT (ng/L) level were evaluated as potential predictors of 30-day mortality.

Cumulative survival curves (Kaplan-Meier curves and estimates of survival data) were constructed to demonstrate differences in event-free survival (all-cause mortality), and a linear model was also constructed to demonstrate the relationship between the hs-cTnT level (ng/L) and the predicted probability of death.

Secondary analyses were performed in 116 (13.2% of the entire cohort) nonconsecutive patients who had a preoperative hs-cTnT sample to evaluate the impact of changes in hs-cTnT regarding mortality. We also evaluated the metrics associated with mortality in VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation).¹⁴

All tests were 2-sided, and a $P < 0.05$ was designated as statistically significant. Analyses were performed using the IBM SPSS Statistical Package v.22 (IBM Corporation, Armonk, NY). When appropriate, the assumptions underlying the use of Cox proportional hazard models were tested. The authors had full access to the data and assume full responsibility for their integrity. All authors have read and have agreed on the final version of the manuscript.

Additional Analyses

Additional analyses were performed to test the hs-cTnT in 2 different scenarios, first as a categorical variable using a threshold of 14 ng/L as a cutoff value for 30-day mortality, and second using age and sex-specific URLs from the literature as described above. Renal function based on the Chronic Kidney Disease Epidemiology Collaboration equation was also tested

in regression models as a continuous (mL/min per 1.73 m^2) and as a categorical variable (estimated glomerular filtration rate $>$ and < 60 mL/min per 1.73 m^2).

RESULTS

The demographics, hospital length of stay, and 30-day mortality of the 876 consecutive patients are shown in Table 1. The patient's American Society of Anesthesiologists Physical Status Classification System, surgery time (minutes), and types of surgery are reported in Table 2. Patient flow is shown in

Table 1. Baseline Characteristics of the Patients Undergoing Noncardiac Surgery

| Baseline Characteristics | Overall Population (N=876) | |
|--|----------------------------|-----------------------------|
| | Valid | Median (25th–75th) or n (%) |
| Age, y | 876 | 63 (54–71) |
| 40–64 y | 876 | 481 (54.9) |
| 65–74 y | 876 | 252 (28.8) |
| ≥ 75 y | 876 | 143 (16.3) |
| Male sex | 876 | 416 (47.5) |
| Non-White | 858 | 64 (7.5) |
| Weight, kg | 783 | 70 (61–80) |
| Height, cm | 205 | 166 (160–172) |
| SBP, mm Hg | 863 | 130 (120–140) |
| DBP, mm Hg | 862 | 80 (70–85) |
| Heart rate, bpm | 868 | 76 (68–85) |
| Heart rate < 60 bpm | 868 | 70 (8.1) |
| Heart rate 60 to 99 bpm | 868 | 740 (85.3) |
| Heart rate ≥ 100 bpm | 868 | 52 (6.0) |
| High blood pressure | 872 | 382 (43.8) |
| Diabetes mellitus | 874 | 127 (14.5) |
| COPD | 876 | 16 (1.8) |
| Smoking | 876 | 73 (8.3) |
| Cardiovascular disease* | 876 | 54 (6.2) |
| Baseline SCr, mg/dL | 808 | 0.9 (0.7–1.1) |
| CDK-EPI, mL/min per 1.73 m^2 | 808 | 84 (61–97) |
| Stage 1 (≥ 90) | 808 | 309 (38.2) |
| Stage 2 (60–89) | 808 | 308 (38.1) |
| Stage 3a (45–59) | 808 | 105 (13.0) |
| Stage 3b (30–44) | 808 | 54 (6.7) |
| Stage 4 and 5 (< 30) | 808 | 32 (4.0) |
| CKD-EPI < 60 mL/min per 1.73 m^2 | 808 | 188 (23.3) |
| Hospital length of stay | 876 | 5 (3–10) |
| 30-d mortality | 876 | 37 (4.2) |

CKD- bpm indicates beats per minute; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EPI, Chronic Kidney Disease Epidemiology Collaboration; SBP, systolic blood pressure; and SCr, serum creatinine.

*Cardiovascular disease means cerebrovascular accident, transient ischemic attack, myocardial infarction, and/or peripheral artery disease.

Figure 1. The Standards for Reporting of Diagnostic Accuracy Studies classification is shown in Table S1.

Hs-cTnT measurements are reported in Table 3. The demographics of those with and without increases in hs-cTnT by survivor status are shown in Table S2, surgical features in Table S3, and the hs-cTnT values in Table S4. The median postoperative hs-cTnT was 10 ng/L (interquartile range, 5–20). Thirty-seven percent of the patients had hs-cTnT values above the overall URL (>14 ng/L), and 25.3% of the patients had values above the age- and sex-specific URLs. One hundred four patients had hs-cTnT above the overall but below the age- and sex-specific URL, representing 11.9% of the overall patients. Of the 116 (13.2%) of the patients who had baseline hs-cTnT samples, only 28 (24%) were increased >14 ng/L. In the group with baseline samples, 24 patients (20.7%) manifested a significant change in hs-cTnT (+12 ng/L; interquartile range, –17 to 26). Detailed hs-cTnT data are shown in Table S4.

Mortality

No patients were lost during follow-up. Death up to 30 days after surgery occurred in 37 patients (4.2%). Mortality was lower after major gynecologic/urologic surgery (1.4%) and higher after major vascular surgery

Table 2. Surgery Feature of the Patients Undergoing Noncardiac Surgery

| Surgery Feature | Overall Population (N=876) | |
|---|----------------------------|-----------------------------|
| | Valid | Median (25th–75th) or n (%) |
| Elective surgery | 876 | 868 (99.1) |
| ASA physical status classification system | | |
| ASA 1 | 876 | 104 (11.9) |
| ASA 2 | 876 | 511 (58.3) |
| ASA 3 | 876 | 225 (25.7) |
| ASA 4 | 876 | 33 (3.8) |
| ASA 5 | 876 | 3 (0.3) |
| ASA >2 | 876 | 261 (29.8) |
| Surgery time, min | 876 | 215 (160–286) |
| Tertile of surgery duration | | |
| First (<175 min) | 876 | 286 (32.6) |
| Second (175–259 min) | 876 | 290 (33.1) |
| Third (≥260 min) | 876 | 300 (34.2) |
| Type of surgery | | |
| Vascular | 876 | 35 (4.0) |
| Gastrointestinal | 876 | 214 (24.4) |
| Neurosurgery | 876 | 112 (12.8) |
| Orthopedic | 876 | 203 (23.2) |
| Gynecologic/urologic | 876 | 288 (32.9) |
| Thoracic | 876 | 24 (2.7) |

ASA indicates The American Society of Anesthesiologists Physical Status classification system.

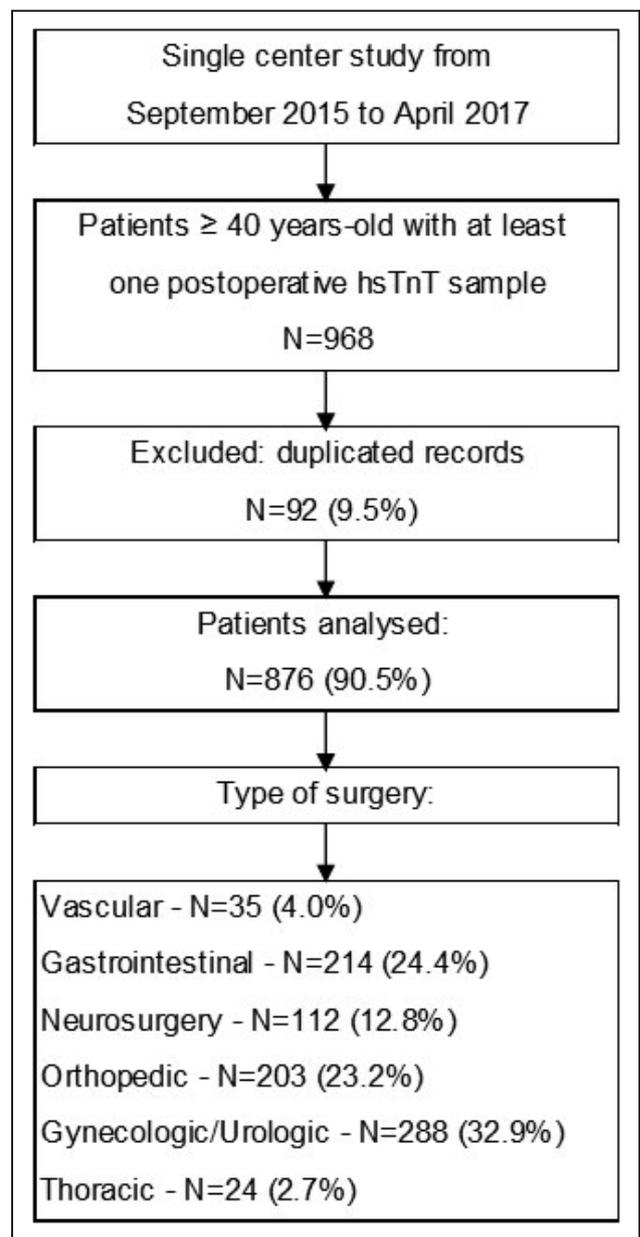


Figure 1. Patients included in the trial.

(8.6%). Patients 40 to 64 years of age had a mortality of 2.3%, while those ≥75 years of age had a mortality of 12.6%. In patients 65 to 74 years of age, mortality was 3.2%. There was no statistically significant relationship between mortality and the duration of surgery, but patients with American Society of Anesthesiologists Physical Status Classification System >2 had higher mortality (11.1% versus 1.3%; *P*<0.001).

Mortality was 1.1% (n=6) among patients with a postoperative hs-cTnT level ≤14 ng/L (n=550; 63% of the population), while in those with hs-cTnT >14 ng/L (n=326; 37% of the population) the mortality was 9.5% (n=31). Two hundred twenty-two patients (25.3%) had

Table 3. hs-cTnT Results of the Patients Undergoing Noncardiac Surgery

| hs-cTnT | Overall Population (N=876) | |
|--|----------------------------|-----------------------------|
| | Valid | Median (25th–75th) or n (%) |
| Baseline hs-cTnT measurement | 876 | 116 (13.2) |
| Baseline hs-cTnT, ng/L* | 116 | 7 (4 to 14) |
| Baseline hs-cTnT >14 ng/L* | 116 | 28 (24.1) |
| Baseline hs-cTnT above age and sex-specific URL | 116 | 20 (17.2) |
| First postoperative hs-cTnT, ng/L | 876 | 10 (5 to 20) |
| Absolute delta hs-cTnT† | 116 | 1 (–2 to 5) |
| Total delta hs-cTnT | 116 | 24 (20.7) |
| Negative delta hs-cTnT | 116 | 10 (8.6) |
| Positive delta hscTnT | 116 | 14 (12.1) |
| Undetectable 1st postoperative hscTnT (<3 ng/L) | 876 | 129 (14.7) |
| 1st postoperative hscTnT >14 ng/L | 876 | 326 (37.2) |
| Age and sex specific URL | 876 | 222 (25.3) |
| hscTnT >14 ng/L and below age and sex specific URL | 876 | 104 (11.9) |

hs-cTnT indicates high-sensitivity cardiac troponin T.

*116 patients had hscTnT measurements before surgery.

†In patients with an additional baseline hs-cTnT measurement a rising pattern (delta hs-cTnT) was considered as a rise or fall of hs-cTnT with at least one value above the 99th percentile OF URL.⁶ For hs-cTnT at values below or close to the 99th percentile of URL, increases above the URL with relative increases of at least >50% or absolute increases of >7 ng/L were used as delta hs-cTnT.^{19,20}

hs-cTnT levels above the age- and sex-specific URL on the first postoperative day. Of those, 1.7% of the deaths were in patients with levels below the adjusted URL and 11.7% in those above the adjusted URL. Patients with hs-cTnT above the overall URL but below the age- and sex-specific URL had no significant increase in mortality ($P=0.793$). Renal function did not impact mortality, but patients with preoperative sinus tachycardia (heart rate >100 beats per minute) had

higher mortality (12.7%) in comparison with patients without tachycardia.

The distribution of our patients compared with those in VISION¹⁴ is shown in Table 4. None of the patients with undetectable hs-cTnT (<3 ng/L) on the first postoperative day died. In the subgroup of patients who had hs-cTnT measured preoperatively, those with the baseline hs-cTnT below the overall URL (≤ 14 ng/L) had a mortality of 1.1%, while in those with elevated baseline hs-cTnT (>14 ng/L), the mortality was 10.7% ($P=0.043$). The patients with a significant change in hs-cTnT (>7 ng/L) had an increase in mortality (16.7%), while none of the patients without a significant change in hs-cTnT died.

Multivariable Cox Proportional Hazards Model

In multivariable Cox proportional hazards analysis, age ≥ 75 years, heart rate >100 bpm, thoracic surgery, American Society of Anesthesiologists Physical Status Classification System >2, and the postoperative hs-cTnT (ng/L) level were independent predictors of 30-day mortality (Table 5). For each 1 ng/L increase in hs-cTnT after surgery, there was a 0.3% increase in mortality ($P<0.001$). Model details are shown in Table S5. Using hs-cTnT as a dichotomous variable, there was an independent association with mortality at 30 days with both the overall URL (HR, 3.19; 95% CI, 1.20–8.49; $P=0.020$) and the age- and sex-specific URLs (HR, 2.76; 95% CI, 1.29–5.91; $P=0.009$). The area under the curve for predicting mortality was 0.89 with continuous data and 0.86 using the cutoff data from VISION.

Logistic regression modeling to predict 30-day mortality found hs-cTnT as a continuous variable (model 1) as well as a categorical variable (using the general URL [99th percentile; model 2] and age- and sex-specific URLs [model 3] to dichotomize the patients) (Table 6). Demographic and surgical characteristics by age and sex are shown in Tables S6 and S7. Tests of the full

Table 4. Post operative (PO) hs-cTnT Values Stratified Using VISION Strata* Assessing PO hs-cTnT Thresholds Associated With 30-Day Mortality

| hs-cTnT Thresholds | n (%) | Death, n (%) | Adjusted HR† | 95% CI | P Value |
|--------------------|------------|--------------|--------------|--------------|---------|
| <5 ng/L | 206 (23.5) | 1 (0.5) | 1.0 | | |
| 5 to <14 ng/L | 333 (38.0) | 5 (1.5) | 1.68 | 0.19–14.58 | 0.637 |
| 14 to <20 ng/L | 111 (12.7) | 5 (4.5) | 2.88 | 0.33–25.57 | 0.341 |
| 20 to <65 ng/L | 180 (20.5) | 13 (7.2) | 4.07 | 0.50–32.91 | 0.188 |
| 65 to <1000 ng/L | 44 (5.0) | 12 (27.3) | 11.56 | 1.40–95.88 | 0.023 |
| ≥ 1000 ng/L | 2 (0.2) | 1 (50.0) | 145.75 | 8.10–2622.26 | 0.001 |

HR indicates hazard ratio; hs-cTnT, high-sensitivity cardiac troponin T; and VISION, Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

*The VISION Cohort Study¹⁴ found the following prevalence of patients in each stratum: peak PO hs-cTnT level <5 ng/L (5318 patients; 24.4%), peak PO hs-cTnT levels of 5 to <14 ng/L (8750 patients; 40.1%), 14 to <20 ng/L (2530 patients/11.6%), 20 to <65 ng/L (4049 patients/18.6%), 65 to <1000 ng/L (1118 patients; 5.1%) and 1000 ng/L or higher (54 patients; 0.2%), with respective 30-day mortality of 0.1% 0.5% 1.1% 3.0% 9.1%, and 29.6%.

†Adjusted for age, sex, and cardiovascular disease.

Table 5. Univariate and Multivariable Cox Proportional Hazards Models—HR and 95% CIs for Predictors of 30-Day Mortality After Noncardiac Surgery (Absolute hs-cTnT Value)

| All Patients | Univariate | | | Multivariate | | |
|---|------------|-------------|---------|--------------|-------------|---------|
| | HR | 95% CI | P Value | HR | 95% CI | P Value |
| Age ≥75 y | 3.59 | 1.88–6.85 | <0.001 | 2.47 | 1.24–4.93 | 0.011 |
| Heart rate >100 bpm | 3.15 | 1.43–6.95 | 0.004 | 3.03 | 1.35–6.79 | 0.007 |
| High blood pressure | 1.94 | 0.97–3.87 | 0.060 | | | |
| Vascular surgery | 2.65 | 0.81–8.67 | 0.107 | | | |
| Thoracic surgery | 4.15 | 0.98–17.53 | 0.053 | 6.07 | 1.37–26.88 | 0.018 |
| CDK-EPI, mL/min per 1.73 m ² | 0.99 | 0.98–1.00 | 0.103 | | | |
| ASA >2 | 3.74 | 1.67–8.37 | 0.001 | 3.33 | 1.34–8.27 | 0.010 |
| hs-cTnT, ng/L | 1.002 | 1.001–1.003 | <0.001 | 1.003 | 1.002–1.005 | <0.001 |

ASA indicates The American Society of Anesthesiologists Physical Status classification system; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; hs-cTnT, high-sensitivity cardiac troponin T; and HR, hazard ratio.

model against a constant-only model (Omnibus Tests of Model Coefficients) in the 3 scenarios were statistically significant, indicating that the predictors as a set reliably distinguished between alive and deceased patients ($P < 0.001$ for all). All models showed good calibration (ie, the agreement between observed and predicted risk) with the Hosmer-Lemeshow test using 10 groups $P > 0.05$ and discrimination (ie, the ability of the test to correctly classify those with and without the disease) with the area under the receiver operating characteristic curve of 0.89, 0.86 and 0.87, respectively (Table 6). Renal function as a predictor of 30-day mortality in the regression models did not change any result when used as a continuous (absolute level in mL/min per 1.73 m²) or as a categorical variable (> and <60 mL/min per 1.73 m²). Model details predicated on age- and sex-specific cutoff values are shown in Tables S8 and S9.

Kaplan-Meier Curves and Linear Model

Figures 2 and 3 show the Kaplan-Meier cumulative survival rate for 30-day mortality based on 2 postoperative hs-cTnT thresholds: hs-cTnT above and below the overall URL and above and below the age- and sex-specific URL.¹⁸ The mean cumulative survival

rate estimated by Kaplan-Meier survival analysis was longer in groups with hs-cTnT below the URLs. Within the first 30 days, a significant difference in all-cause death rate was observed between both groups (84.9% versus 66.4% and 84.0% versus 60.6%, respectively; $P < 0.001$ at log rank for both).

Both Pearson *r* and Spearman rho showed that there was a significant monotonic component of the relationship between the first postoperative hs-cTnT (ng/L) level and the predicted probability of death. The linear model was significant, with $R^2 = 0.483$ while the quadratic model had an $R^2 = 0.487$, showing a very small increase, explaining only an additional 0.4% of the variance in the hs-cTnT predicting the probability of death. Because of that, we rejected the quadratic model and adopted a linear model (Figure 4).

DISCUSSION

Our data add new information to this emerging field. To the best of our knowledge, this is the first study that has evaluated hs-cTnT as a continuous variable to determine its relationship to 30-day mortality in patients undergoing noncardiac surgery. Using multivariable Cox proportional hazards model, we demonstrated

Table 6. Multivariate Logistic Regression Model Testing hs-cTnT as a Continuous Variable (First Model) as Well as a Categorical Variable (We Used the 99th Percentile of URL [Second Model] and Age- and Sex-Specific URL [Third Model] to Dichotomize the Patients)

| | Logistic Regression | | | | Calibration | Discrimination | |
|--------------|------------------------|---------|---------------------------|--------------------|----------------------|----------------|-----------|
| | Test of the Full Model | | Nagelkerke R ² | Prediction Success | Hosmer-Lemeshow Test | C-Statistic | |
| | Chi-Square | P Value | | % | P Value | AUC | 95% CI |
| First model | 79 580 | <0.001 | 0.308 | 96.0 | 0.958 | 0.89 | 0.85–0.94 |
| Second model | 67 766 | <0.001 | 0.264 | 95.5 | 0.313 | 0.86 | 0.81–0.92 |
| Third model | 68 251 | <0.001 | 0.266 | 95.1 | 0.508 | 0.87 | 0.81–0.92 |

AUC indicates area under the curve; hs-cTnT, high-sensitivity cardiac troponin T; and URL, upper reference limit.

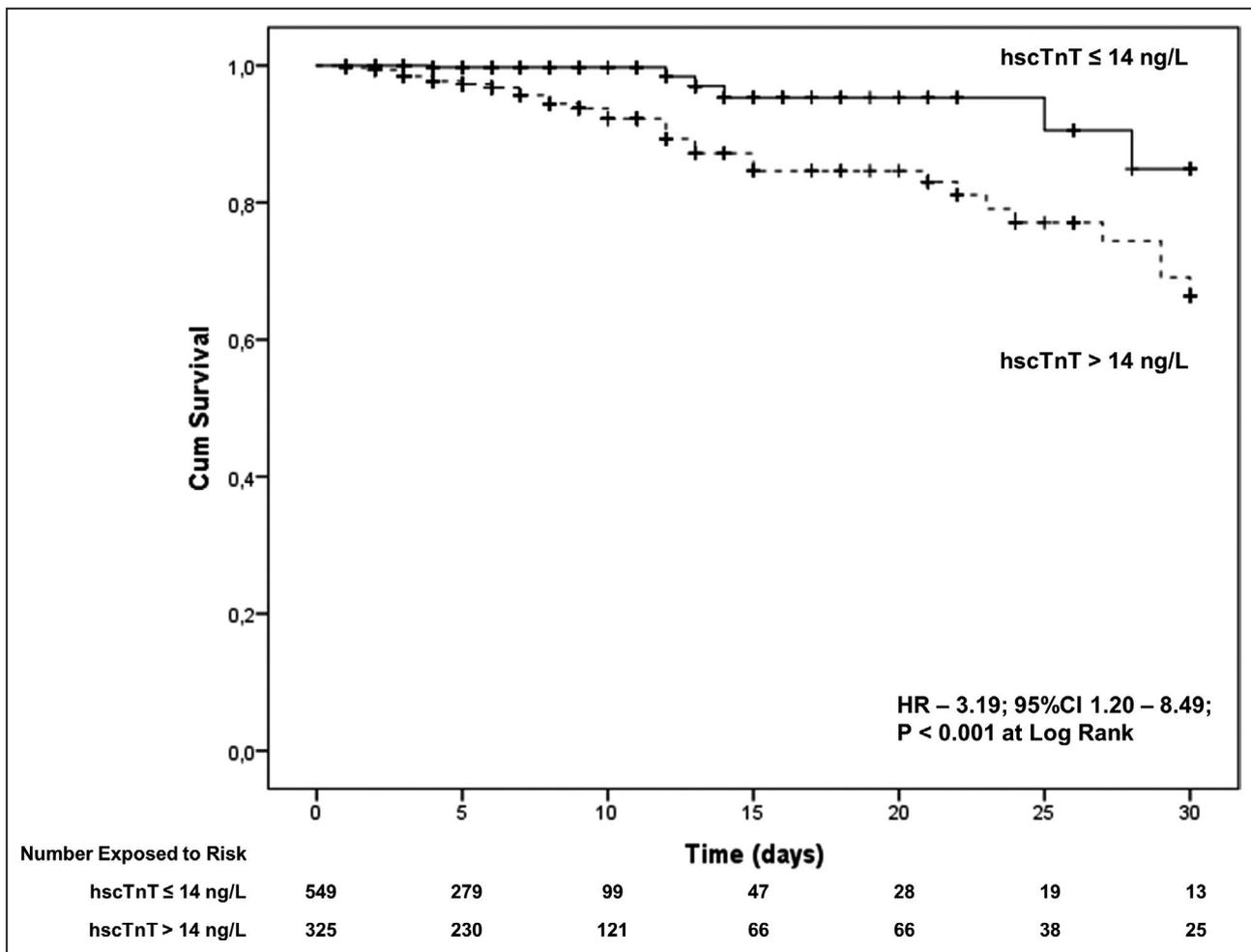


Figure 2. Survival based on an overall hs-cTnT cutoff value of 14 n/L was used; $P < 0.001$ by log rank. HR indicates hazard ratio; and hs-cTnT, high-sensitivity cardiac troponin T.

that the hs-cTnT level after surgery is an independent predictor of all-cause 30-day mortality. For each 1 ng/L increase in hs-cTnT after surgery, there was a 0.3% increase in mortality (HR, 1.003; 95% CI, 1.002–1.005; $P < 0.001$). Although the CIs overlapped, this approach manifested the best the area under receiver operating characteristic curve (0.89) in comparison with the use of single cutoff options for defining isolated myocardial injury (0.86 and 0.87, respectively) (Table 6). These data suggest a dose-response relationship between hs-cTnT and 30-day mortality using the categorical cutoff values as seen in VISION.¹⁴ Mortality ranged from 3.0% (peak postoperative hs-cTnT levels of 20 to <65 ng/L) to 29.6% (peak postoperative hs-cTnT levels of ≥ 1000 ng/L). They are also similar to the data from Puelacher et al,¹⁵ who demonstrated a near-linear relationship between mortality and hs-cTnT concentrations > 10 ng/L. In our analysis, we also observed a near-linear pattern with a significant monotonic component of the relationship between the first postoperative hs-cTnT level (ng/L) and predicted probability of

death (Figure 3). This approach with continuous data has been used by others^{20,23–25} in different clinical settings with similar results. These findings may have important implications for clinical practice as hs-cTnT is a quantitative test that may be useful in determining the urgency of diagnostic and therapeutic responses in individual patients. This, of course, does not imply that all increases are associated with the same risk. While we provide the comparative data from VISION, clinicians can elect to use a cutoff value instead, which we provide in Table 4, recognizing that it will invariably lack either sensitivity or specificity.

Additionally, this is also the first study to evaluate age- and sex-specific URLs in this clinical setting. They were independently associated with a higher 30-day mortality rate, with HR of 2.76 (95% CI, 1.29–5.91; $P = 0.009$) in comparison with patients without a postoperative hs-cTnT increase based on this cutoff value (11.7% versus 1.7%, respectively; $P < 0.001$). Although our Cox analysis showed a significant association between the overall URL and mortality, a

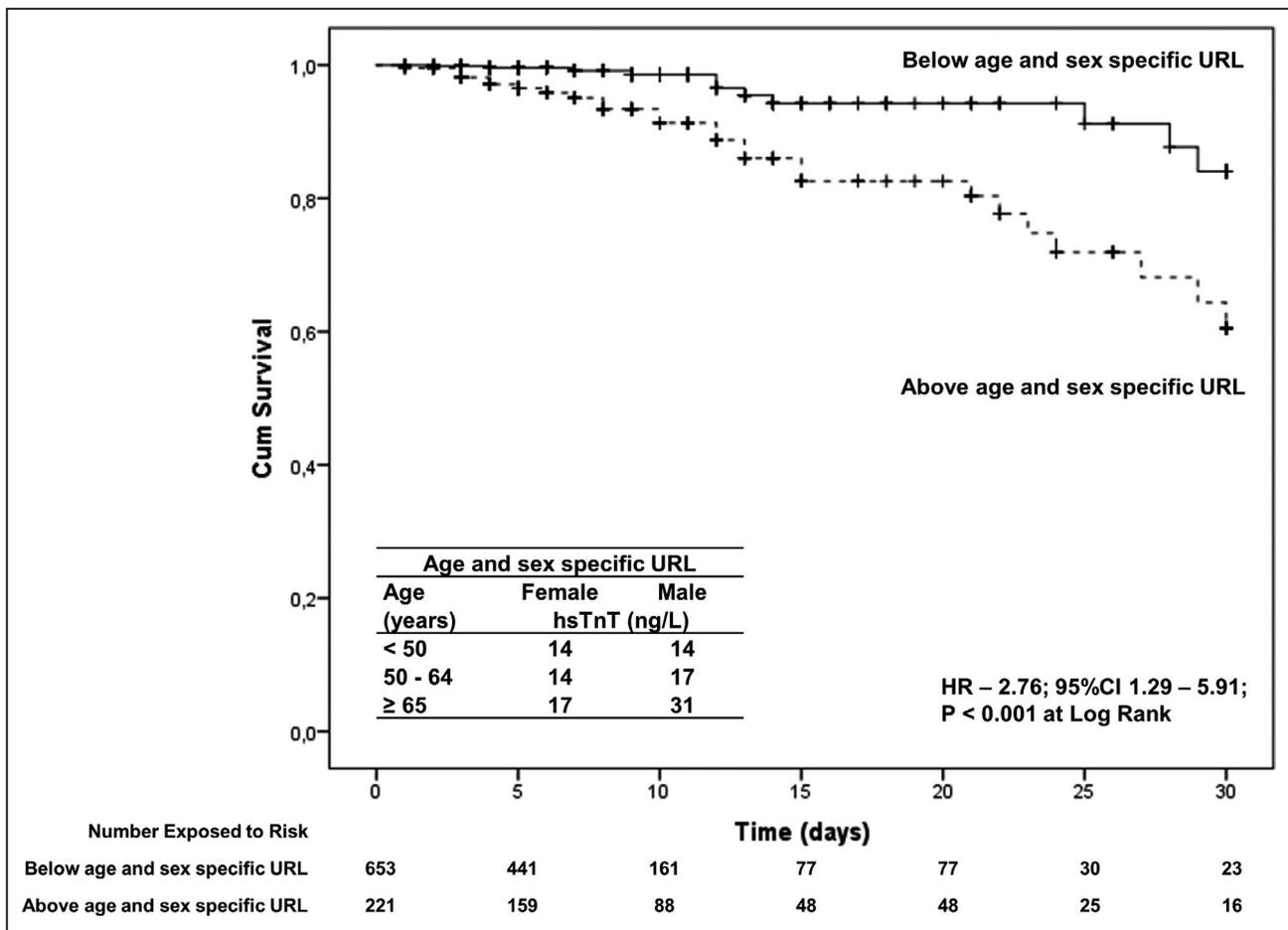


Figure 3. Survival based on age- and sex-specific hs-cTnT cutoff values; $P < 0.001$ by log rank. HR indicates hazard ratio; hs-cTnT high-sensitivity cardiac troponin T; and URL, upper reference limit.

secondary analysis of the 104 patients (11.9% of the entire cohort) diagnosed with values greater than the overall URL (>14 ng/L) but not by the age- and sex-specific URL showed no significant increase in mortality ($P=0.793$). One could argue that a significant number of patients might have been overdiagnosed using the overall URL. Others also have suggested that women may be better classified using a sex-specific cutoff value.^{10,26} This approach may take into account the fact that women have lower normal values than men at any given age but are also, as a group, older in most data sets, which causes some increases in their normal values. Taking both of these considerations into account may be important. It is also conceivable that the use of higher cutoff values in this group corrects the lack of a baseline value by ignoring the minor changes that can occur postoperatively even in normal subjects.²⁷ However, the area under the receiver operating characteristic curve analysis showed only nonsignificant improvement (Figure 5). This could be attributable to a lack of power to observe this phenomenon, but more data about this issue are needed.

In our study, only a small group had preoperative associated with postoperative hs-cTnT measurements allowing delta analysis. This is unfortunate but is the present state of the art. There is no mandate for obtaining a routine baseline sample in preoperative surgical patients, leaving clinicians often in the situation of interpreting an isolated postoperative value. We are advocates for obtaining such values in all patients. In our small subset with baseline values as in other investigations, evaluation of delta was highly predictive of risk. This was also the case in VISION¹⁴; absolute hs-cTnT change of ≥ 5 ng/L was also associated with an increased risk of 30-day mortality (adjusted HR, 4.69; 95% CI, 3.52–6.25). A baseline sample is also helpful in identifying those apt to have postoperative increases and thus specifically acute events.^{10,28} If there is no change from baseline, then likely a conservative approach that incorporates knowledge of the structural abnormalities that may explain the observed increase may be all that is necessary in these cases. However, if a significant increase is present, then there may be the potential to intervene acutely depending on the etiology of the increases

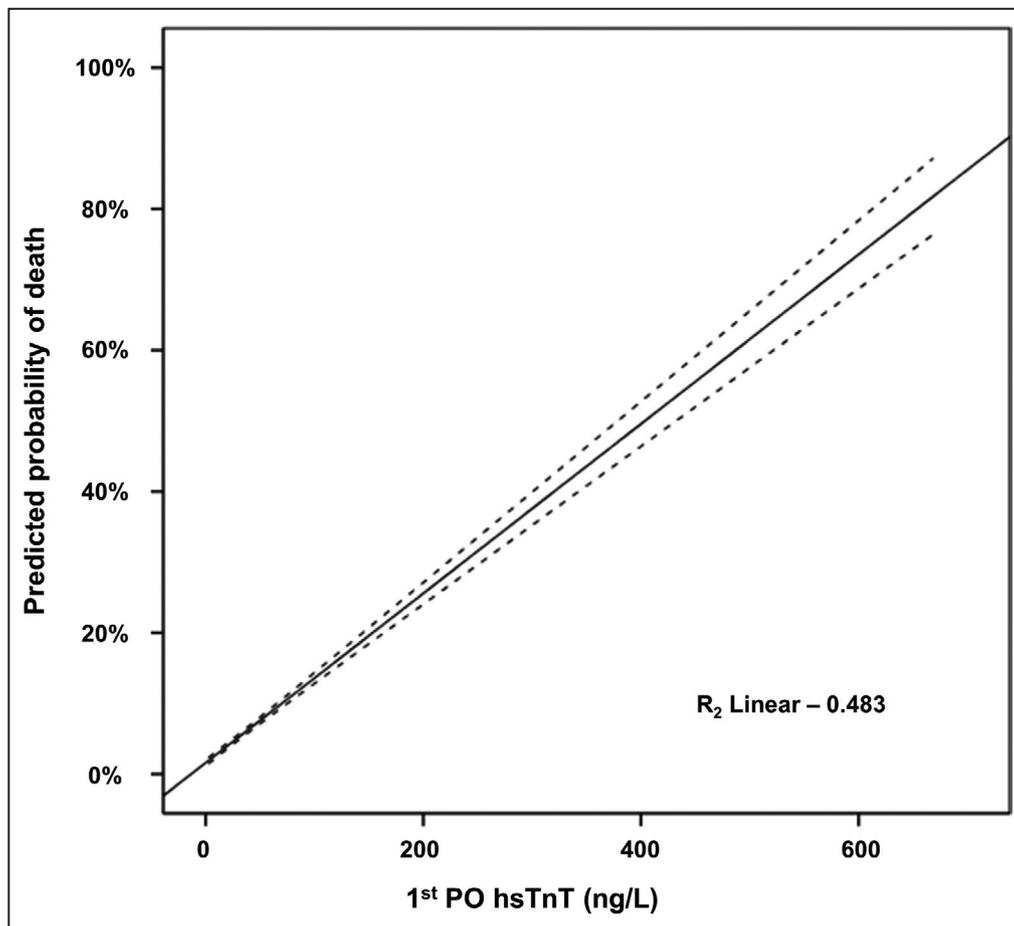


Figure 4. Linear and quadratic regression for the relationship between first postoperative hs-cTnT value after noncardiac surgery and predicted probability of death. hs-cTnT indicates high-sensitivity cardiac troponin T; and PO, postoperative.

defined clinically. We hope that further analysis of the MANAGE (Management of Myocardial Injury After Noncardiac Surgery) trial,²⁹ which suggested that the benefit of dabigatran in these patients will inform us more about whether the apparent benefit of this agent was in those with chronic structural disease or with acute events.

Our data are similar to those of other studies in this arena. Our data look very similar overall to the data from VISION.¹⁴ In prior studies,^{9–15} the incidence of patients with hs-cTnT >14 ng/L postoperatively ranged from 11.3% to 64.4%.^{12,13} Although many would argue that these increases were attributable to myocardial infarction, this diagnosis ranged from 8.6% to 12.2% because most of such patients do not manifest symptoms and/or definitive ECG changes.^{10,13}

How should clinicians use these data? The benefit of a continuous relationship is that clinicians can choose which cutoff values they wish to use in any given case. Using values above or below the sex-specific cutoff values distinguishes a group with a mortality of 1.7% from that with a mortality of 11.7%, so some clinicians

may wish to use these cut points. Higher values such as the ones used in VISION are associated with still higher mortality, ranging from an odds ratio for death of 2.88 (14–20 ng/L) to 4.07 (20–65 ng/L) to 11.56 (65–1000 ng/L) and 145.75 (>1000 ng/L) although, given the small numbers, these bins were not always statistically significantly more prognostic in our data set. However, in any given case, the clinician can interdigitate the available clinical information with the hs-cTnT values to decide how to proceed or not in a way that is much more effective than using fixed thresholds. It may be that in some cases, values near but not above those thresholds might occur, and it should be reassuring to clinicians that even if the threshold is not exceeded that the risk is very high. Thus, the cutoffs indicated above are guideposts for consideration, not mandates. This is common in other clinical situations such as acute coronary syndromes and the critically ill; higher values portend a worse prognosis. These data can in the long run be used in a Bayesian manner. We anticipate that in the long term, these could be incorporated into such

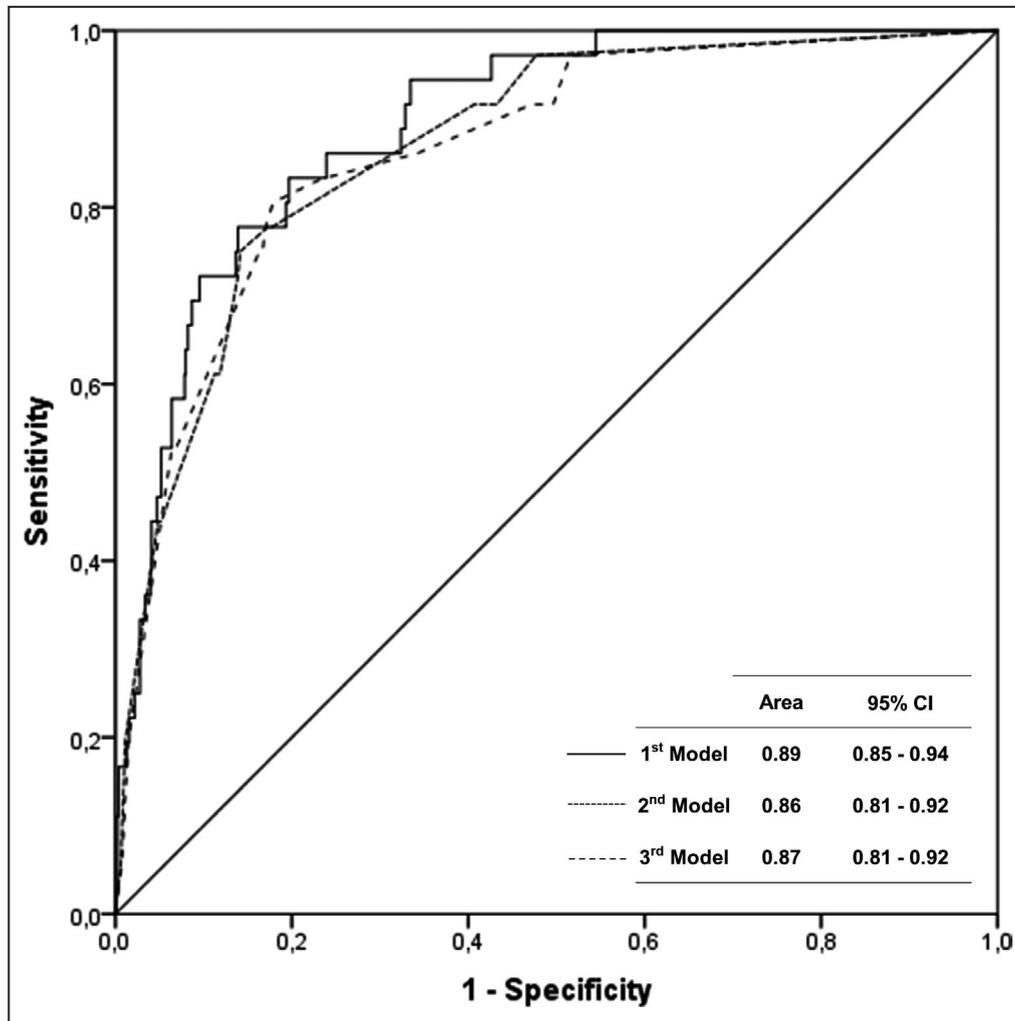


Figure 5. Receiver operating characteristic curve analysis comparing the predicted probability for all-cause mortality according to the first postoperative hs-cTnT (ng/L) level (first model), the 99th percentile of URL (second model), and age and sex-specific URL (third model) after noncardiac surgery.

hs-cTnT indicates high-sensitivity cardiac troponin T; and URL, upper reference limit.

an approach with artificial intelligence on the basis of the hs-cTnT value and the perioperative risk score.

It is unclear what the response should be to a diagnosis of postoperative myocardial injury. First and foremost, one needs to determine the etiology of the hs-cTnT increase and treat it accordingly. If pulmonary embolism is present, anticoagulation is indicated. If the increase is attributable to sepsis, then primary attention to infection is mandated. It is likely that the etiology of the increase will in many cases be related to the cause of the mortality. If no etiology is clear because it is thought that many of these events are ischemic in nature, secondary prevention following MI is always a good approach.⁶ Might there be benefit from the intervention in a subset? Smilowitz et al³⁰ evaluated 34 650 patients with perioperative acute MI detected without hs-cTnT assays and

demonstrated that invasive management with cardiac catheterization or coronary revascularization was associated with lower mortality than conservative management (8.9% versus 18.1%; $P < 0.001$) with an odds ratio of 0.44 (95% CI, 0.41–0.47). However, he studied a highly selected group identified by clinical characteristics. Likely, some of these were larger events, as hs-cTn assays were not used. Are these sorts of patients in our population? No doubt they are. If it is likely that such patients are those with more marked increases of hs-cTnT and those with larger delta hs-cTnT change. We do not advocate intervention in all such patients but would suggest that for those who want to consider such an approach, those with more marked hs-cTnT values and more change are the ones on which to focus. That group, instead of having type 2 MIs, may have type

1 events, which is what is found in 50% of patients in autopsy studies.^{6,31,32}

Study Limitations

This study has several limitations. First of all, this is a single-center study and the selection of the noncardiac surgery population may not be representative of the general surgical population. As an observational study, only patients who had an hs-cTnT sample on the morning of the first postoperative day were included in the analysis, which may represent an additional selection bias. Because we have had only one sample of hs-cTnT on the first day after surgery, a myocardial injury that may have occurred after that time interval was missed. Furthermore, we were not able to differentiate between cardiovascular and noncardiovascular deaths. However, most events following noncardiac surgery are thought to be ischemic and attributable to type 2 MI,³³ though we should note that, after an autopsy, many type 1 events may be revealed.^{6,31,32} In addition, we did not have N-terminal pro-B-type natriuretic peptide measurements, which have recently been shown to help define pre- and postoperative risk.³⁴ Finally, we lacked a baseline sample in most patients, and only a small group had preoperative hs-cTnT measurements allowing delta analysis, which in many studies helps to identify risk.^{10,29}

CONCLUSIONS

In this population of patients undergoing noncardiac surgery, a single hs-cTnT measurement at the first postoperative day, evaluated as a continuous variable, was an independent predictor of 30-day mortality with the best area under the receiver operating characteristic curve. The categorized hs-cTnT elevation using the general URL (99th percentile) or the age- and sex-specific URL were also associated with death at 30 days, but a subgroup of patients with hs-cTnT above the general URL but below the age- and sex-specific URL had no significant increase in mortality. As an alternative approach, age- and sex-specific URL may be a more suitable option than the general URL in this clinical setting.

ARTICLE INFORMATION

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Dr Jaffe has in the past or presently consults for most of the major diagnostic companies including the company that makes the cardiac troponin assay used in this study. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S9

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Supplemental Material

Table S1. STARD Checklist.

| Section & Topic | No | Item | Reported on page # |
|--------------------------|------------|--|--------------------|
| TITLE OR ABSTRACT | | | |
| | 1 | Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) | 1-3 |
| ABSTRACT | | | |
| | 2 | Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) | 3 |
| INTRODUCTION | | | |
| | 3 | Scientific and clinical background, including the intended use and clinical role of the index test | 4 |
| | 4 | Study objectives and hypotheses | 4 |
| METHODS | | | |
| <i>Study design</i> | 5 | Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) | 4 |
| <i>Participants</i> | 6 | Eligibility criteria | 4 |
| | 7 | On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) | 4 |
| | 8 | Where and when potentially eligible participants were identified (setting, location and dates) | 4 |
| | 9 | Whether participants formed a consecutive, random or convenience series | 4 |
| <i>Test methods</i> | 10a | Index test, in sufficient detail to allow replication | 4-5 |
| | 10b | Reference standard, in sufficient detail to allow replication | 4-5 |

| | | | |
|---------------------|------------|--|-----|
| | 11 | Rationale for choosing the reference standard (if alternatives exist) | 4-5 |
| | 12a | Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory | 4-5 |
| | 12b | Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory | 4-6 |
| | 13a | Whether clinical information and reference standard results were available to the performers/readers of the index test | N/A |
| | 13b | Whether clinical information and index test results were available to the assessors of the reference standard | N/A |
| <i>Analysis</i> | 14 | Methods for estimating or comparing measures of diagnostic accuracy | 5-6 |
| | 15 | How indeterminate index test or reference standard results were handled | N/A |
| | 16 | How missing data on the index test and reference standard were handled | 4-5 |
| | 17 | Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory | 5-6 |
| | 18 | Intended sample size and how it was determined | N/A |
| RESULTS | | | |
| <i>Participants</i> | 19 | Flow of participants, using a diagram | 4 |
| | 20 | Baseline demographic and clinical characteristics of participants | 6 |
| | 21a | Distribution of severity of disease in those with the target condition | 6-7 |
| | 21b | Distribution of alternative diagnoses in those without the target condition | 6-7 |
| | 22 | Time interval and any clinical interventions between index test and reference standard | N/A |
| <i>Test results</i> | 23 | Cross tabulation of the index test results (or their distribution) by the results of the reference standard | N/A |

| | | | |
|--------------------------|-----------|---|------|
| | 24 | Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) | 7-8 |
| | 25 | Any adverse events from performing the index test or the reference standard | N/A |
| DISCUSSION | | | |
| | 26 | Study limitations, including sources of potential bias, statistical uncertainty, and generalisability | 10 |
| | 27 | Implications for practice, including the intended use and clinical role of the index test | 8-10 |
| OTHER INFORMATION | | | |
| | 28 | Registration number and name of registry | N/A |
| | 29 | Where the full study protocol can be accessed | N/A |
| | 30 | Sources of funding and other support; role of funders | 2 |

**Table S2. Baseline characteristics of the patients undergoing non cardiac surgery
by survivor status.**

| Baseline Characteristics | n | Overall population (n = 876) | n | Survivors (n = 839) | N | Nonsurvivors (n = 37) | P Value |
|---------------------------------------|-------|---|-------|---|-------|---|---------|
| | Valid | Median (25 th - 75 th) or n (%) | Valid | Median (25 th - 75 th) or n (%) | Valid | Median (25 th - 75 th) or n (%) | |
| Age (years) | 876 | 63.0 (54.0 - 71.0) | 839 | 63.0 (53.0 - 70.0) | 37 | 74.0 (62.0 - 80.5) | <0.001 |
| 40 to 64 years | 876 | 481 (54.9) | 839 | 470 (56.0) | 37 | 11 (29.7) | 0.002 |
| 65 to 74 years | 876 | 252 (28.8) | 839 | 244 (29.1) | 37 | 8 (21.6) | 0.327 |
| ≥ 75 years | 876 | 143 (16.3) | 839 | 125 (14.9) | 37 | 18 (48.6) | <0.001 |
| Male Sex | 876 | 416 (47.5) | 839 | 395 (47.1) | 37 | 21 (56.8) | 0.249 |
| Non-caucasian | 858 | 64 (7.5) | 821 | 61 (7.4) | 37 | 3 (8.1) | 0.751 |
| Weight (kg) | 783 | 70.0 (61.0 - 80.0) | 754 | 70.0 (61.0 - 80.0) | 29 | 65.0 (57.0 - 76.5) | 0.057 |
| Height (cm) | 205 | 166 (160 - 172) | 202 | 167 (160 - 172) | 3 | 165 (155 -) | 0.572 |
| SBP (mmHg) | 863 | 130 (120 - 140) | 827 | 130 (120 - 140) | 36 | 130 (110 - 140) | 0.588 |
| DBP (mmHg) | 862 | 80 (70 - 85) | 826 | 80 (70 - 85) | 36 | 80 (66 - 90) | 0.890 |
| Heart Rate (bpm) | 868 | 76 (68 - 85) | 832 | 76 (68 - 85) | 36 | 84 (68 - 95) | 0.012 |
| Heart Rate < 60 bpm | 868 | 70 (8.1) | 832 | 70 (8.4) | 36 | 0 (0.0) | 0.107 |
| Heart Rate 60 to 99 bpm | 868 | 740 (85.3) | 832 | 712 (85.6) | 36 | 28 (77.8) | 0.196 |
| Heart Rate ≥ 100 bpm | 868 | 52 (6.0) | 832 | 44 (5.3) | 36 | 8 (22.2) | 0.001 |
| High Blood Pressure | 872 | 382 (43.8) | 835 | 357 (42.8) | 37 | 25 (67.6) | 0.003 |
| Diabetes Mellitus | 874 | 127 (14.5) | 837 | 122 (14.6) | 37 | 5 (13.5) | 0.858 |
| COPD | 876 | 16 (1.8) | 839 | 15 (1.8) | 37 | 1 (2.7) | 0.502 |
| Smoking | 876 | 73 (8.3) | 839 | 70 (8.3) | 37 | 3 (8.1) | 1.000 |
| Cardiovascular Disease† | 876 | 54 (6.2) | 839 | 49 (5.8) | 37 | 5 (13.5) | 0.071 |
| Baseline SCr (mg/dL) | 808 | 0.9 (0.7 - 1.1) | 771 | 0.9 (0.7 - 1.1) | 37 | 0.9 (0.7 - 1.5) | 0.346 |
| CDK-EPI (mL/min/1.73m ²) | 808 | 84.0 (61.0 - 97.0) | 771 | 84.0 (61.0 - 97.0) | 37 | 75.0 (37.5 - 93.5) | 0.122 |
| Stage 1 (≥ 90) | 808 | 309 (38.2) | 771 | 297 (38.5) | 37 | 12 (32.4) | 0.457 |
| Stage 2 (60 – 89) | 808 | 308 (38.1) | 771 | 294 (38.1) | 37 | 14 (37.8) | 0.971 |
| Stage 3a (45 – 59) | 808 | 105 (13.0) | 771 | 104 (13.5) | 37 | 1 (2.7) | 0.075 |
| Stage 3b (30 - 44) | 808 | 54 (6.7) | 771 | 49 (6.4) | 37 | 5 (13.5) | 0.093 |
| Stage 4 and 5 (<30) | 808 | 32 (4.0) | 771 | 27 (3.5) | 37 | 5 (13.5) | 0.012 |
| CKD-EPI <60 mL/min/1.73m ² | 808 | 188 (23.3) | 771 | 177 (23.0) | 37 | 11 (29.7) | 0.341 |
| Hospital Length of Stay | 876 | 5 (3 - 10) | 839 | 5 (3 - 9) | 37 | 12 (6 - 22) | <0.001 |
| 30-day Mortality | 876 | 37 (4.2) | 839 | 0 (0.0) | 37 | 37 (100.0) | - |

SBP - systolic blood pressure; DBP - diastolic blood pressure; COPD - chronic obstructive pulmonary disease; SCr - serum creatinine; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration.

*Cardiovascular disease means cerebrovascular accident, transient ischemic attack, myocardial infarction and/or peripheral artery disease.

Table S3. Surgery features of the patients undergoing noncardiac surgery according to survivor status.

| Surgery feature | n | Overall population (n = 876) | n | Survivors (n = 839) | n | Nonsurvivors (n = 37) | P Value |
|----------------------------------|-------|---|-------|---|-------|---|---------|
| | Valid | Median (25 th - 75 th) or n (%) | Valid | Median (25 th - 75 th) or n (%) | Valid | Median (25 th - 75 th) or n (%) | |
| Elective Surgery | 876 | 868 (99.1) | 839 | 834 (99.4) | 37 | 34 (91.9) | 0.003 |
| ASA 1 | 876 | 104 (11.9) | 839 | 103 (12.3) | 37 | 1 (2.7) | 0.113 |
| ASA 2 | 876 | 511 (58.3) | 839 | 504 (60.1) | 37 | 7 (18.9) | <0.001 |
| ASA 3 | 876 | 225 (25.7) | 839 | 208 (24.8) | 37 | 17 (45.9) | 0.004 |
| ASA 4 | 876 | 33 (3.8) | 839 | 22 (2.6) | 37 | 11 (29.7) | <0.001 |
| ASA 5 | 876 | 3 (0.3) | 839 | 2 (0.2) | 37 | 1 (2.7) | 0.122 |
| ASA > 2 | 876 | 261 (29.8) | 839 | 232 (27.7) | 37 | 29 (78.4) | <0.001 |
| Surgery Time (min) | 876 | 215 (160 - 286) | 839 | 210 (160 - 285) | 37 | 240 (155 - 323) | 0.307 |
| First (< 175 min) | 876 | 286 (32.6) | 839 | 275 (32.8) | 37 | 11 (29.7) | 0.699 |
| Second (175 to 259 min) | 876 | 290 (33.1) | 839 | 281 (33.5) | 37 | 9 (24.3) | 0.246 |
| Third (≥ 260 min) | 876 | 300 (34.2) | 839 | 283 (33.7) | 37 | 17 (45.9) | 0.125 |
| Vascular Surgery | 876 | 35 (4.0) | 839 | 32 (3.8) | 37 | 3 (8.1) | 0.180 |
| Gastrointestinal Surgery | 876 | 214 (24.4) | 839 | 202 (24.1) | 37 | 12 (32.4) | 0.247 |
| Neurologic Surgery | 876 | 112 (12.8) | 839 | 104 (12.4) | 37 | 8 (21.6) | 0.125 |
| Orthopedic Surgery | 876 | 203 (23.2) | 839 | 195 (23.2) | 37 | 8 (21.6) | 0.819 |
| Gynecological/Urological Surgery | 876 | 288 (32.9) | 839 | 284 (33.8) | 37 | 4 (10.8) | 0.004 |
| Thoracic surgery | 876 | 24 (2.7) | 839 | 22 (2.6) | 37 | 2 (5.4) | 0.269 |

*ASA - The American Society of Anesthesiologists Physical Status classification system

Table S4. hsTnT results of the patients undergoing noncardiac surgery according to survivor status.

| hsTnT | n | Overall population (n = 876) | n | Survivors (n = 839) | n | Nonsurvivors (n = 37) | P Value |
|---------------------------------------|-------|---|-------|---|-------|---|---------|
| | Valid | Median (25 th - 75 th) or n (%) | Valid | Median (25 th - 75 th) or n (%) | Valid | Median (25 th - 75 th) or n (%) | |
| hsTnT | | | | | | | |
| Baseline hsTnT measurement | 876 | 116 (13.2) | 839 | 112 (13.3) | 37 | 4 (10.8) | 0.807 |
| Baseline hsTnT (ng/L) † | 116 | 7.49 (3.53 - 13.74) | 112 | 7.14 (3.24 - 13.44) | 4 | 38.46 (15.88 - 113.03) | 0.010 |
| Baseline hsTnT Above 14 ng/L † | 116 | 28 (24.1) | 112 | 25 (22.3) | 4 | 3 (75.0) | 0.043 |
| Baseline hsTnT Above A&G-D URL | 116 | 20 (17.2) | 112 | 17 (15.2) | 4 | 3 (75.0) | 0.016 |
| 1°PO hsTnT (ng/L) | 876 | 9.72 (5.00 - 20.04) | 839 | 9.30 (4.70 - 18.90) | 37 | 38.22 (17.55 - 97.82) | <0.001 |
| Absolute Delta hsTnT ‡ | 116 | 0.8 (-1.7 - 5.0) | 112 | 0.7 (-1.7 - 4.6) | 4 | 106.9 (-8.5 - 266.2) | 0.082 |
| Total Delta Troponin (FBR) (Y/N) | 116 | 24 (20.7) | 112 | 20 (17.9) | 4 | 4 (100.0) | 0.001 |
| Negative Delta Troponin (Y/N) | 116 | 10 (8.6) | 112 | 9 (8.0) | 4 | 1 (25.0) | 0.003 |
| Positive Delta Troponin (Y/N) | 116 | 14 (12.1) | 112 | 11 (9.8) | 4 | 3 (75.0) | 0.005 |
| Relative delta hsTnT § (1°PO/14ng/L) | 121 | 0.1 (-0.1 - 0.4) | 117 | 0.1 (-0.1 - 0.4) | 4 | 7.6 (-0.6 - 19.0) | 0.082 |
| Undetectable 1°PO hsTnT (<3 ng/L) | 876 | 129 (14.7) | 839 | 129 (15.4) | 37 | 0 (0.0) | 0.010 |
| 1°PO TnT hs > 14 ng/L | 876 | 326 (37.2) | 839 | 295 (35.2) | 37 | 31 (83.8) | <0.001 |
| Age- and Sex-dependent URL | 876 | 222 (25.3) | 839 | 196 (23.4) | 37 | 26 (70.3) | <0.001 |
| hsTnT > 14 ng/L and below A&G-D URL † | 876 | 104 (11.9) | 839 | 99 (11.8) | 37 | 5 (13.5) | 0.752 |

*116 patients had hsTnT measurement before surgery.

†A&G-D - Age- and Sex-dependent URL

‡In patients with an additional baseline hsTnT measurement a rising pattern (delta hsTnT) was considered as a rise and/or fall of hsTnT with at least one value above the 99th percentile of URL.⁶

For hsTnT at values below or close to the 99th percentile of URL, increases above the URL with relative increases of at least > 50% or absolute increases of > 7 ng/L were used as delta hsTnT.^{19,20}

Table S5. Univariate and multivariable Cox proportional hazards models –

Hazard Ratio and 95% confidence intervals for predictors of 30-day mortality after noncardiac

surgery (99th percentile of URL).

| | Univariate | | | Multivariate | | |
|--------------------------------------|------------|--------------|---------|--------------|--------------|---------|
| | HR | 95%CI | P-Value | HR | 95%CI | P-Value |
| All patients | | | | | | |
| Age ≥ 75 years | 3.59 | 1.88 – 6.85 | <0.001 | 2.69 | 1.36 – 5.31 | 0.004 |
| Heart rate > 100 bpm | 3.15 | 1.43 – 6.95 | 0.004 | 2.63 | 1.18 – 5.87 | 0.018 |
| High blood pressure | 1.94 | 0.97 – 3.87 | 0.060 | | | |
| Vascular surgery | 2.65 | 0.81 – 8.67 | 0.107 | | | |
| Thoracic surgery | 4.15 | 0.98 – 17.53 | 0.053 | 4.77 | 1.10 – 20.75 | 0.037 |
| CKD-EPI (mL/min/1.73m ²) | 0.99 | 0.98 – 1.00 | 0.103 | | | |
| ASA > 2 | 3.74 | 1.67 – 8.37 | 0.001 | 2.48 | 1.03 – 5.95 | 0.043 |
| hscTnT > 14 ng/L | 4.60 | 1.90 – 11.13 | 0.001 | 3.19 | 1.20 – 8.49 | 0.020 |

CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; ASA - The American Society of Anesthesiologists Physical Status classification system.

Table S6. Baseline characteristics of the patients undergoing noncardiac surgery based on age and sex-specific URL.

| Baseline Characteristics | n | Overall population (n = 876) | Below age and sex specific URL (n = 654) | Above age and sex specific URL (n = 222) | P Value |
|--|-----|---------------------------------|---|---|------------|
| | | Valid | Median (25 th - 75 th) or n (%) | Median (25 th - 75 th) or n (%) | |
| Age (years) | 876 | 63.0 (54.0 - 71.0) | 62.0 (52.0 - 69.0) | 67.0 (60.0 - 79.0) | <0.001 |
| 40 to 64 years | 876 | 481 (54.9) | 385 (58.9) | 96 (43.2) | <0.001 |
| 65 to 74 years | 876 | 252 (28.8) | 202 (30.9) | 50 (22.5) | 0.017 |
| ≥ 75 years | 876 | 143 (16.3) | 67 (10.2) | 76 (34.2) | <0.001 |
| Male sex | 876 | 416 (47.5) | 332 (50.8) | 84 (37.8) | 0.001 |
| Non-caucasian | 858 | 64 (7.5) | 48 (7.5) | 16 (7.4) | 0.973 |
| Weight (kg) | 783 | 70.0 (61.0 - 80.0) | 70.0 (63.0 - 80.0) | 70.0 (59.0 - 80.0) | 0.037 |
| Height (cm) | 205 | 166 (160 - 172) | 167 (160 - 172) | 165 (160 - 170) | 0.203 |
| SBP (mmHg) | 863 | 130 (120 - 140) | 130 (120 - 140) | 130 (120 - 140) | 0.824 |
| DBP (mmHg) | 862 | 80 (70 - 85) | 80 (70 - 85) | 80 (70 - 85) | 0.643 |
| Heart rate (bpm) | 868 | 76 (68 - 85) | 75 (68 - 85) | 78 (68 - 88) | 0.056 |
| Heart rate < 60 bpm | 868 | 70 (8.1) | 52 (8.0) | 18 (8.1) | 0.978 |
| Heart rate 60 to 99 bpm | 868 | 740 (85.3) | 557 (86.2) | 183 (82.4) | 0.169 |
| Heart rate ≥ 100 bpm | 868 | 52 (6.0) | 32 (5.0) | 20 (9.0) | 0.028 |
| High blood pressure | 872 | 382 (43.8) | 258 (39.6) | 124 (56.1) | <0.001 |
| Diabetes Mellitus | 874 | 127 (14.5) | 88 (13.5) | 39 (17.6) | 0.128 |
| COPD | 876 | 16 (1.8) | 9 (1.4) | 7 (3.2) | 0.141 |
| Smoking | 876 | 73 (8.3) | 57 (8.7) | 16 (7.2) | 0.482 |
| Cardiovascular disease* | 876 | 54 (6.2) | 21 (3.2) | 33 (14.9) | <0.001 |
| Baseline SCr (mg/dL) | 808 | 0.9 (0.7 - 1.1) | 0.8 (0.7 - 1.0) | 1.0 (0.7 - 1.4) | <0.001 |
| CDK-EPI (mL/min/1.73m ²) | 808 | 84.0 (61.0 - 97.0) | 87.0 (69.0 - 99.0) | 61.0 (42.5 - 89.0) | <0.001 |
| Stage 1 (≥ 90) | 808 | 309 (38.2) | 258 (43.7) | 51 (23.5) | <0.001 |
| Stage 2 (60 – 89) | 808 | 308 (38.1) | 248 (42.0) | 60 (27.6) | <0.001 |
| Stage 3a (45 – 59) | 808 | 105 (13.0) | 59 (10.0) | 46 (21.2) | <0.001 |
| Stage 3b (30 - 44) | 808 | 54 (6.7) | 17 (2.9) | 37 (17.1) | <0.001 |
| Stage 4 and 5 (<30) | 808 | 32 (4.0) | 9 (1.5) | 23 (10.6) | <0.001 |
| CKD-EPI < 60 mL/min/1.73m ² | 808 | 188 (23.3) | 83 (14.0) | 105 (48.4) | <0.001 |
| Hospital length of stay | 876 | 5 (3 - 10) | 5 (3 - 8) | 8 (4 - 14) | <0.001 |
| 30-day mortality | 876 | 37 (4.2) | 11 (1.7) | 26 (11.7) | <0.001 |

SBP – systolic blood pressure; DBP – diastolic blood pressure; COPD – chronic obstructive pulmonary disease; SCr – serum creatinine; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration.

*Cardiovascular disease means cerebrovascular accident, transient ischemic attack, myocardial infarction, and/or peripheral artery disease.

Table S7. Surgery feature of the patients undergoing noncardiac surgery based on age and sex-specific URL.

| Surgery Feature | n | Overall population (n = 876) | Below age and sex specific URL (n = 654) | Above age and sex specific URL (n = 222) | P Value |
|---|-----|---------------------------------|---|---|------------|
| | | Valid | Median (25 th - 75 th) or n (%) | Median (25 th - 75 th) or n (%) | |
| Elective surgery | 876 | 868 (99.1) | 650 (99.4) | 218 (98.2) | 0.118 |
| ASA physical status classification system* | | | | | |
| ASA 1 | 876 | 104 (11.9) | 93 (14.2) | 11 (5.0) | <0.001 |
| ASA 2 | 876 | 511 (58.3) | 413 (63.1) | 98 (44.1) | <0.001 |
| ASA 3 | 876 | 225 (25.7) | 132 (20.2) | 93 (41.9) | <0.001 |
| ASA 4 | 876 | 33 (3.8) | 15 (2.3) | 18 (8.1) | <0.001 |
| ASA 5 | 876 | 3 (0.3) | 1 (0.2) | 2 (0.9) | 0.160 |
| ASA > 2 | 876 | 261 (29.8) | 148 (22.6) | 113 (50.9) | <0.001 |
| Surgery time (min) | 876 | 215 (160 - 286) | 210 (160 - 285) | 230 (169 - 305) | 0.043 |
| Tertile of surgery duration | | | | | |
| First (< 175 min) | 876 | 286 (32.6) | 226 (34.6) | 60 (27.0) | 0.039 |
| Second (175 to 259 min) | 876 | 290 (33.1) | 209 (32.0) | 81 (36.5) | 0.215 |
| Third (≥ 260 min) | 876 | 300 (34.2) | 219 (33.5) | 81 (36.5) | 0.416 |
| Type of surgery | | | | | |
| Vascular | 876 | 35 (4.0) | 17 (2.6) | 18 (8.1) | <0.001 |
| Gastrointestinal | 876 | 214 (24.4) | 161 (24.6) | 53 (23.9) | 0.824 |
| Neurosurgery | 876 | 112 (12.8) | 93 (14.2) | 19 (8.6) | 0.029 |
| Orthopedic | 876 | 203 (23.2) | 120 (18.3) | 83 (37.4) | <0.001 |
| Gynecologic/Urologic | 876 | 288 (32.9) | 244 (37.3) | 44 (19.8) | <0.001 |
| Thoracic | 876 | 24 (2.7) | 19 (2.9) | 5 (2.3) | 0.607 |

*ASA - The American Society of Anesthesiologists Physical Status classification system

Table S8. Results of the patients undergoing noncardiac surgery based on age and sex-specific URL.

| hscTnT | n | Overall population (n = 876) | Below age and sex specific URL (n = 654) | Above age and sex specific URL (n = 222) | P Value |
|--|-----|---------------------------------|---|---|------------|
| | | Valid | Median (25 th - 75 th) or n (%) | Median (25 th - 75 th) or n (%) | |
| Baseline hscTnT measurement | 876 | 116 (13.2) | 87 (13.3) | 29 (13.1) | 0.927 |
| Baseline hscTnT (ng/L)* | 116 | 7 (4 - 14) | 6 (3 - 11) | 25 (10 - 46) | <0.001 |
| Baseline hscTnT > 14 ng/L* | 116 | 28 (24.1) | 10 (11.5) | 18 (62.1) | <0.001 |
| Baseline hscTnT above age and sex specific URL | 116 | 20 (17.2) | 3 (3.4) | 17 (58.6) | <0.001 |
| 1 st postoperative hscTnT (ng/L) | 876 | 10 (5 - 20) | 7 (4 - 11) | 33 (22 - 58) | <0.001 |
| Absolute delta hscTnT† | 116 | 1 (-2 - 5) | 0 (-1 - 3) | 11 (-6 - 18) | 0.009 |
| Total delta hscTnT | 116 | 24 (20.7) | 3 (3.4) | 21 (72.4) | <0.001 |
| Negative delta hscTnT | 116 | 10 (8.6) | 3 (3.4) | 7 (24.1) | 0.002 |
| Positive delta hscTnT | 116 | 14 (12.1) | 0 (0.0) | 14 (48.3) | <0.001 |
| Undetectable 1 st postoperative hscTnT (<3 ng/L) | 876 | 129 (14.7) | 129 (19.7) | 0 (0.0) | <0.001 |
| 1 st postoperative hscTnT > 14 ng/L | 876 | 236 (37.2) | 104 (15.9) | 222 (100.0) | <0.001 |
| Age and sex specific URL | 876 | 222 (25.3) | 0 (0.0) | 222 (100.0) | <0.001 |
| VISION Strata | | | | | |
| < 5 ng/L | 876 | 219 (25.0) | 219 (33.5) | 0 (0.0) | <0.001 |
| 5 to < 14 ng/L | 876 | 331 (37.8) | 331 (50.6) | 0 (0.0) | <0.001 |
| 14 to < 20 ng/L | 876 | 106 (12.1) | 66 (10.1) | 40 (18.0) | 0.002 |
| 20 to < 65 ng/L | 876 | 174 (19.9) | 38 (5.8) | 136 (61.3) | <0.001 |
| 65 to < 1000 ng/L | 876 | 44 (5.0) | 0 (0.0) | 44 (19.8) | <0.001 |
| ≥ 1000 ng/L | 876 | 2 (0.2) | 0 (0.0) | 2 (0.9) | 0.064 |

*116 patients had hscTnT measurement before surgery.

†In patients with an additional baseline hscTnT measurement a rising pattern (delta hscTnT) was considered as a rise and/or fall of hscTnT with at least one value above the 99th percentile OF URL.⁶

For hscTnT values below or close to the 99th percentile of URL, increases above the URL with relative increases of at least > 50% or absolute increases of > 7 ng/L were used as delta hscTnT.^{19,20}

Table S9. Univariate and multivariable Cox proportional hazards models – Hazard Ratio and 95% confidence intervals for predictors of 30-day mortality after noncardiac surgery (age and sex-specific URL).

| | Univariate | | | Multivariate | | |
|--------------------------------------|------------|--------------|---------|--------------|-------------|---------|
| | HR | 95%CI | P-Value | HR | 95%CI | P-Value |
| All patients | | | | | | |
| Age ≥ 75 years | 3.59 | 1.88 – 6.85 | <0.001 | 2.65 | 1.34 – 5.25 | 0.005 |
| Heart rate > 100 bpm | 3.15 | 1.43 – 6.95 | 0.004 | 2.73 | 1.22 – 6.10 | 0.014 |
| High blood pressure | 1.94 | 0.97 – 3.87 | 0.060 | | | |
| Vascular surgery | 2.65 | 0.81 – 8.67 | 0.107 | | | |
| Thoracic surgery | 4.15 | 0.98 – 17.53 | 0.053 | | | |
| CDK-EPI (mL/min/1.73m ²) | 0.99 | 0.98 – 1.00 | 0.103 | | | |
| ASA > 2 | 3.74 | 1.67 – 8.37 | 0.001 | 2.49 | 1.03 – 6.04 | 0.043 |
| Age and sex specific URL | 3.92 | 1.92 – 7.98 | <0.001 | 2.76 | 1.29 – 5.91 | 0.009 |

CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; ASA - The American Society of Anesthesiologists Physical Status classification system.