



Prognostic Role of High-sensitivity Cardiac Troponin I and Soluble Suppression of Tumorigenicity-2 in Surgical Intensive Care Unit Patients Undergoing Non-cardiac Surgery

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Background: The prognostic utility of cardiac biomarkers, high-sensitivity cardiac troponin I (hs-cTnI) and soluble suppression of tumorigenicity-2 (sST2), in non-cardiac surgery is not well-defined. We evaluated hs-cTnI and sST2 as predictors of 30-day major adverse cardiac events (MACE) in patients admitted to the surgical intensive care unit (SICU) following major non-cardiac surgery.

Methods: hs-cTnI and sST2 concentrations were measured in 175 SICU patients immediately following surgery and for three days postoperatively. The results were analyzed in relation to 30-day MACE and were compared with the revised Goldmann cardiac risk index (RCRI) score.

Results: Overall, 30-day MACE was observed in 16 (9.1%) patients. hs-cTnI and sST2 concentrations differed significantly between the two groups with and without 30-day MACE ($P < 0.05$). The maximum concentration of sST2 was an independent predictor of 30-day MACE (odds ratio = 1.016, $P = 0.008$). The optimal cut-off values of hs-cTnI and sST2 for predicting 30-day MACE were 53.0 ng/L and 182.5 ng/mL, respectively. A combination of hs-cTnI and sST2 predicted 30-day MACE better than the RCRI score. Moreover, 30-day MACE was observed more frequently with increasing numbers of above-optimal cut-off hs-cTnI and sST2 values ($P < 0.0001$). Reclassification analyses indicated that the addition of biomarkers to RCRI scores improved the prediction of 30-day MACE.

Conclusions: This study demonstrates the utility of hs-cTnI and sST2 in predicting 30-day MACE following non-cardiac surgery. Cardiac biomarkers would provide enhanced risk stratification in addition to clinical RCRI scores for patients undergoing major non-cardiac surgery.

Key Words: High-sensitivity cardiac troponin I, Soluble suppression of tumorigenicity-2, Non-cardiac surgery, Prognosis

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INTRODUCTION

The term “major adverse cardiac events” (MACE) refers to a composite of clinical events; although MACE lacks a standard

definition, it is commonly used to evaluate procedural, short-term, or long-term clinical outcomes [1, 2]. The incidence of 30-day MACE in non-cardiac surgery has been reported to be approximately 10% following major surgery [3]; the risk depends

on patient- and surgery-specific characteristics. Conventional perioperative risk estimation models, such as the revised Goldman cardiac risk index (RCRI), have been applied for patients scheduled to undergo non-cardiac surgery; further cardiac-specific testing, such as echocardiography, stress testing, and cardiac biomarkers, is reserved for patients with known or suspected heart diseases [4–7]. However, risk estimation models remain quite limited in predicting perioperative deaths, and up to half of cardiac deaths occur in patients without prior known heart diseases [8].

Myocardial injury after non-cardiac surgery (MINS), a component of MACE, is defined as troponin T levels of ≥ 0.04 ng/mL; its reported incidence is approximately 8% [9]. One in 10 MINS patients die within 30 days; without troponin monitoring, >80% of MINS events would be missed [9]. The incidence of MINS in vascular surgery patients is 19.1%, and MINS is independently associated with 30-day mortality [10]. The potential role of biomarker monitoring has been examined; the peak troponin T value during the first three days post-surgery is associated with 30-day mortality [11], and elevated postoperative troponin T without an ischemic feature is also associated with 30-day mortality [12]. The use of a high-sensitivity troponin T assay has been reported to increase the perioperative myocardial infarction (MI) detection rate [13]; however, until quite recently, it has been uncertain whether high-sensitivity cardiac troponin I (hs-cTnI) has better predictive power for 30-day morbidity or mortality.

Soluble suppression of tumorigenicity-2 (sST2), a novel biomarker, has demonstrated strong prognostic value in patients with heart failure (HF) [14, 15], acute coronary syndrome [16, 17], chronic hemodialysis [18], and sepsis [19]; however, the prognostic role of sST2 in patients undergoing non-cardiac surgery is unknown.

The purpose of this study was to explore the association between the hs-cTnI and sST2 concentrations and 30-day MACE in patients undergoing major non-cardiac surgery. We examined whether the use of hs-cTnI and sST2 could predict 30-day MACE better than clinical assessment using the RCRI score in these patients. We hypothesized that a cardiac biomarker-based approach would have additive value on top of RCRI score-based clinical judgement. The novelty of this study is that combined hs-cTnI and sST2 analysis was performed for predicting 30-day MACE.

METHODS

1. Study population

This prospective study was approved by the Institutional Review

Board of Konkuk University Medical Center, Seoul, Korea, and was conducted in compliance with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. From June 2014 to May 2015, 1,140 patients underwent major surgery under general anesthesia and were admitted to the surgical intensive care unit (SICU) postoperatively. Of these, we excluded patients younger than 45 years ($N=451$) [9], patients undergoing cardiac surgery ($N=298$), and/or patients who did not provide informed consent preoperatively ($N=145$). In addition, we excluded 71 patients who could not undergo biomarker testing on the day of surgery, immediately postoperatively (D0), or on the following three postoperative days (D1, D2, and D3). A total of 175 patients (age 66 ± 12 years, range 45–92 years; 90 males) were enrolled in this study, and their baseline characteristics are detailed in Table 1. Although there is no standard definition of MACE, we monitored 30-day MACE, including death, non-fatal cardiac arrest, MI, and acute decompensated HF [2]. We compared the serial changes in the biomarkers in patients with or without such events.

2. Assays

hs-cTnI and sST2 concentrations were measured according to the manufacturers' instructions. The blood samples were obtained by venipuncture into serum-separating tubes (Greiner Bio-One GmbH, Frickenhausen, Germany) and were delivered to the laboratory without delay; the sera were separated promptly from whole blood and were stored at -70°C in small aliquots until analysis of each biomarker.

hs-cTnI concentration was measured using the ARCHITECT STAT High Sensitive Troponin-I chemiluminescence immunoassay on an i2000 analyzer (Abbott diagnostics, Abbott Park, IL, USA). sST2 concentration was measured using the Presage ST2 Assay (Critical Diagnostics, San Diego, CA, USA), which is an enzyme-linked immunosorbent assay comprising a ready-to-use 96-well microtiter plate coated with mouse monoclonal anti-human sST2 antibodies and measured using spectrophotometric absorbance at 450 nm with a microtiter well reader [20]. sST2 concentrations were measured in duplicate and the average value of the two measurements was used for statistical analysis. The manufacturer-claimed measurable range of the hs-cTnI assay was 1.0–50,000 ng/L; this assay was designed to have within-laboratory (total) imprecision of 10% coefficient of variation (CV) with controls or panels across this range. The manufacturer-claimed measurable range of the sST2 assays was 3.1–250 ng/mL. The CV (%) of each assay was determined in our laboratory according to the Clinical and Laboratory Standards Institute (CLSI) doc-

Table 1. Characteristics of the study population

Characteristics	N= 175
Age (year)	66 ± 12
Male/Female	90/85
Body mass index (kg/m ²)	23.5 ± 4.3
ASA class	
I	12 (6.9)
II	97 (55.4)
III	52 (29.7)
IV	14 (8.0)
RCRI factors	
High-risk surgery*	98 (56.0)
History of ischemic heart disease	15 (8.6)
History of heart failure	6 (3.4)
History of cerebrovascular disease	18 (10.3)
Preoperative insulin use	5 (2.9)
Preoperative serum creatinine >2.0 mg/dL	12 (6.9)
RCRI score	
0	58 (33.1)
1	90 (51.4)
2	20 (11.4)
3–6	7 (4.0)
In-hospital mortality	7 (4.0)
30-day mortality	6 (3.4)
30-day MACE [†]	16 (9.1)
Hypertension on medications	109 (62.3)
Diabetes mellitus	47 (26.9)
Peripheral vascular disease	4 (2.3)
Atrial fibrillation	12 (6.9)
Urgent/emergent surgery	50 (28.6)
Operation duration, minutes	185 [135–300]
Two concomitant surgeries	11 (6.3)
Surgical specialty [‡]	
General surgery	92 (52.6)
Neurosurgery	57 (32.6)
Orthopedic surgery	17 (9.7)
Gynecologic surgery	3 (1.7)
Vascular surgery	2 (1.1)
Thoracic surgery	2 (1.1)
Others (urology and plastic surgery)	2 (1.1)

Data are presented as mean ± standard deviation, median [interquartile range], or number (%).

*Examples include vascular surgery and any open intraperitoneal or intra-thoracic procedures; [†]A total of 22 MACE events were observed in 16 patients: death (N=6), non-fatal cardiac arrest (N=2), MI (N=5), and acute decompensated HF (N=9). Five patients had two or three MACE: MI and acute decompensated HF in one patient; MI, acute decompensated HF, and cardiac death in one patient; and acute decompensated HF and death in three patients; [‡]In cases with multi-department surgeries, the major surgery was considered.

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; RCRI, revised Goldman cardiac risk index; MACE, major adverse cardiac events; MI, myocardial infarction; HF, heart failure.

ument EP15-A2 [21]. The CVs were tested at two levels by running three replicates over five days; the actual CV (%) of the hs-cTnI and sST2 assays were <4.0% and <3.0%, respectively.

3. Statistical analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range, IQR) depending on data distribution. Normality was tested using Kolmogorov-Smirnov nonparametric tests, and sphericity was tested using Mauchly's test. The Mann-Whitney U test was used to compare values between the two groups with or without 30-day MACE. Univariate and multivariate logistic regression analyses were used to identify predictors of 30-day MACE; variables included age, sex, patient factors in the conventional risk prediction model (RCRI), and biomarkers (hs-cTnI and sST2). With regard to biomarkers, maximum values from the serial measurement (D0 to D3) were used for logistic regression analyses. Odds ratio (OR) was reported with 95% confidence interval (CI). The receiver operating characteristic (ROC) curves of each biomarker and RCRI score were compared to obtain optimal cut-off values for predicting 30-day MACE. Areas under the curves (AUC) were reported with their 95% CI and were assessed as follows: 0.5–0.6, fail; 0.6–0.7, poor; 0.7–0.8, fair; 0.8–0.9, good; 0.9–1.0, excellent. Using the optimal cut-off values obtained from the ROC curve, hs-cTnI and sST2 concentrations were dichotomized (above and below the cut-off values) to compare the proportion of 30-day MACE according to the number of above cut-off values for hs-cTnI and sST2 (0, 1, and 2); the chi-square test was used to compare this proportion. Using the dichotomized variables, the ROC curves of RCRI score, combined biomarkers, and the combination of RCRI score and biomarkers were re-analyzed, and their AUC were compared for prognostic utility [22]. Reclassification analyses using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess the added value of the biomarker approach on top of RCRI score; NRI and IDI values were analyzed with their 95% CI. Maximum values of hs-cTnI and sST2 throughout D0–D3 were used as variables for logistic regression, ROC curve, and reclassification analyses [9].

IBM SPSS Statistics (version 22, Armonk, NY, USA), MedCalc Software (version 17.9, MedCalc Software, Mariakerke, Belgium), and R Statistics (version 3.3.1, The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. *P* values <0.05 were considered statistically significant.

RESULTS

During the 30-day postoperative period, myocardial ischemia was suspected in 26 patients because of chest pain only (N=2) or electrocardiographic ST-T segment changes with or without

coronary angiography (N=24). Coronary angiography was performed for eight of these patients, proving acute coronary syndrome with significant stenosis in five patients. The primary outcome of 30-day MACE was 22 events observed in 16 patients (9%): death (N=6), non-fatal cardiac arrest (N=2), MI (N=5),

Table 2. Distribution of biomarkers between the two groups with or without 30-day major adverse cardiac events

	Total (N=175)	30-day MACE (+) (N=16)	30-day MACE (-) (N=159)	P*
hs-cTnI, ng/L				
POD 0	7.8 [3.0–20.6]	20.0 [6.0–151.7]	7.3 [3.0–19.9]	0.009
POD 1	10.4 [4.8–25.8]	52.4 [16.2–292.0]	9.9 [4.7–22.4]	0.001
POD 2	11.2 [5.0–30.3]	92.1 [17.8–310.9]	10.0 [4.8–28.6]	<0.001
POD 3	9.8 [4.5–29.5]	81.0 [19.3–286.5]	8.4 [4.0–20.0]	<0.001
POD1–POD0	1.60 [–0.40–6.50]	11.9 [0.75–141.4]	1.30 [–0.60–5.30]	0.003
POD2–POD0	1.80 [–0.90–10.30]	30.8 [0.50–244.4]	1.60 [–1.20–9.10]	0.005
POD3–POD0	0.90 [–1.40–7.20]	44.0 [1.18–276.4]	0.60 [–1.40–5.40]	0.005
sST2, ng/mL				
POD 0	45.9 [29.0–107.0]	72.5 [42.2–210.8]	43.0 [29.0–102.0]	0.046
POD 1	155.0 [84.0–219.0]	188.8 [158.2–225.8]	144.0 [79.0–217.0]	0.058
POD 2	79.0 [50.0–158.0]	178.7 [107.3–229.3]	73.0 [46.0–140.0]	<0.001
POD 3	59.5 [33.8–99.3]	118.0 [85.0–252.0]	52.0 [32.8–88.0]	<0.001
POD1–POD0	68.0 [21.0–139.0]	102.4 [–7.8–145.5]	65.0 [21.0–137.0]	0.548
POD2–POD0	21.0 [0.0–65.0]	65.5 [–8.75–135.5]	20.7 [0.0–54.0]	0.165
POD3–POD0	1.0 [–18.0–17.8]	27.0 [–14.0–153.1]	0.0 [–20.0–15.0]	0.029

All data are presented as median and interquartile range.

*30-day MACE (+) vs 30-day MACE (–).

Abbreviations: MACE, major adverse cardiac events; hs-cTnI, high-sensitivity cardiac troponin I; sST2, soluble suppression of tumorigenicity-2; POD, post-operative day.

Table 3. Univariate and multivariate logistic regression analyses for 30-day major adverse cardiac events

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.037 (0.991–1.086)	0.116		
Female	1.065 (0.381–2.977)	0.905		
High-risk surgery	3.100 (1.029–9.343)	0.044	7.152 (0.807–63.420)	0.077
History of ischemic heart disease	6.773 (1.968–23.308)	0.002	11.735 (0.741–185.822)	0.081
History of heart failure	26.127 (4.343–157.670)	<0.001	14.609 (0.885–241.139)	0.061
History of cerebrovascular disease	5.105 (1.538–16.944)	0.008	5.006 (0.356–70.422)	0.232
Diabetes on insulin	2.583 (0.271–24.620)	0.409		
Serum creatinine >2.0 mg/dL	3.846 (0.926–15.976)	0.064		
RCRI score	2.052 (1.212–3.476)	0.008	0.658 (0.127–3.395)	0.617
hs-cTnI, maximum (ng/L)	1.001 (1.001–1.001)	0.032	1.001 (1.001–1.001)	0.029
sST2, maximum (ng/mL)	1.011 (1.003–1.018)	0.004	1.016 (1.004–1.028)	0.008

Abbreviations: RCRI, revised Goldman cardiac risk index; hs-cTnI, high-sensitivity cardiac troponin I; sST2, soluble suppression of tumorigenicity-2; OR, odds ratio; CI, confidence interval.

and acute decompensated HF (N=9). Five patients had two or three MACE: MI and acute decompensated HF in one patient; MI, acute decompensated HF, and cardiac death in one patient, and acute decompensated HF and death in three patients. Time-to-first MACE ranged from D1 to D22 postoperatively (median D3). The RCRI scores were: 0 (N=3); 1 (N=5); 2 (N=6); and 3 (N=2).

Table 2 shows the distribution of hs-cTnI and sST2 in patients with or without 30-day MACE. The concentrations of hs-cTnI and sST2 were significantly higher in patients with 30-day MACE than in patients without such events (all $P < 0.05$), except for the D1 sST2 concentration ($P = 0.058$). The hs-cTnI concentration was elevated in D1 and D2 compared with D0 (10.4 and 11.2 vs 7.8 ng/L; all $P < 0.05$). The sST2 concentration was markedly elevated in D1 compared with D0, D2, and D3 (155.0 vs 45.9, 79.0, and 59.5 ng/mL, all $P < 0.05$). The median values (IQR) of the maximum hs-cTnI and sST2 concentrations in 175 patients

were 15.60 ng/L (7.50–55.20) and 174.0 ng/mL (98.0–233.0), respectively.

Logistic regression analyses demonstrated that the maximum concentrations of hs-cTnI and sST2 were two independent predictors of 30-day MACE (Table 3). ROC curve analyses showed

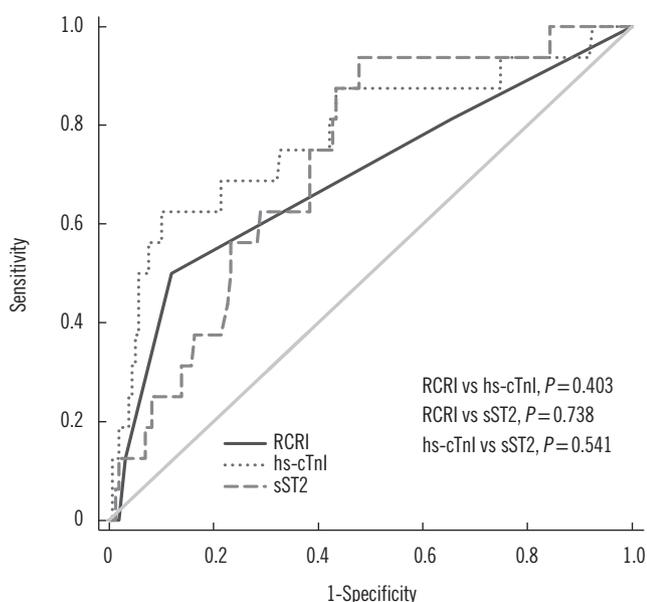


Fig. 1. Receiver operator characteristic curve analyses for the prediction of 30-day MACE in patients following major non-cardiac surgeries. The optimal cut-off value of hs-cTnI (max) for prediction of 30-day MACE was 53.0 ng/L (sensitivity, 68.8% [95% CI, 41.3–89.0%]; specificity, 78.6% [95% CI, 71.4–84.7%]) and that of sST2 (max) was 182.5 ng/mL (sensitivity, 87.5% [95% CI, 61.7–98.5%]; specificity, 56.6% [95% CI, 48.5–64.4%]). hs-cTnI (max) and sST2 (max) demonstrated fair predictive ability for 30-day MACE compared with the poor ability of RCRI score, although there was no statistical difference between the AUCs.

Abbreviations: MACE, major adverse cardiac events; CI, confidence interval; RCRI, revised Goldman cardiac risk index; hs-cTnI, high-sensitivity cardiac troponin I; sST2, soluble suppression of tumorigenicity-2; AUC, area under the curve.

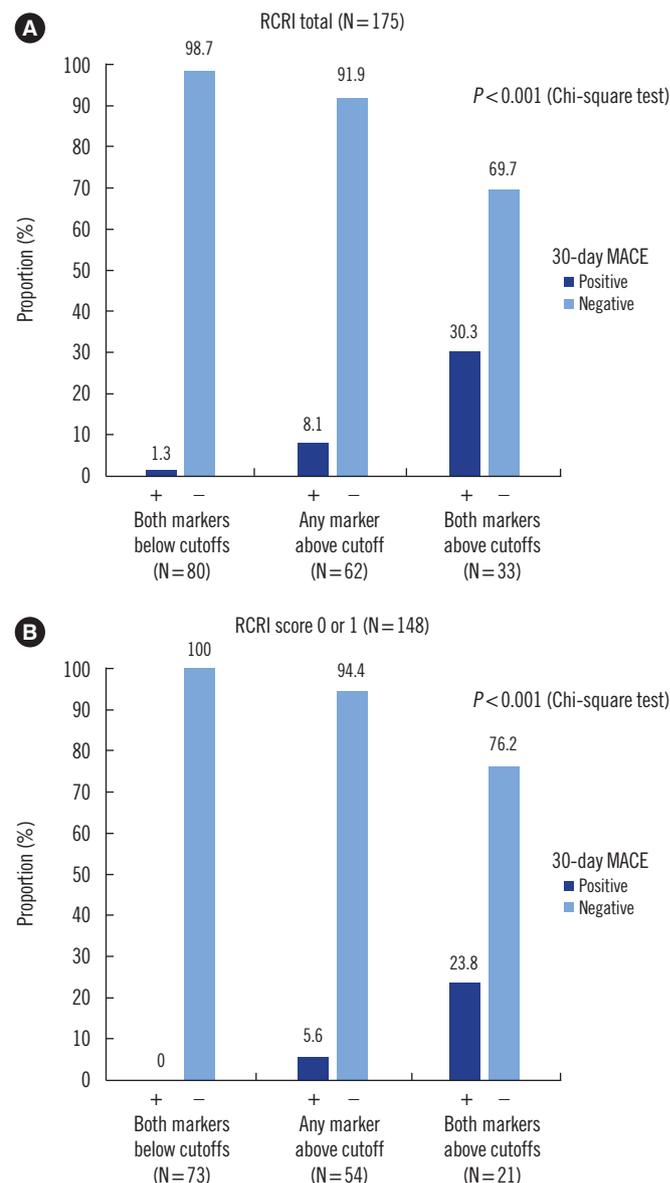


Fig. 2. Thirty-day MACE according to the number of hs-cTnI and sST2 above cut-off values (53.0 ng/L and 182.5 ng/mL, respectively). (A) Overall, 30-day MACE was observed more frequently as the number of above cut-off values increased ($P < 0.001$). (B) This finding was also observed in 148 patients with an RCRI score of 0 or 1 ($P < 0.001$).

Abbreviations: MACE, major adverse cardiac events; CI, confidence interval; RCRI, revised Goldman cardiac risk index; hs-cTnI, high-sensitivity cardiac troponin I; sST2, soluble suppression of tumorigenicity-2; AUC, area under the curve.

Table 4. Reclassification analyses using integrated discrimination improvement and net reclassification improvement

	AUC (95% CI)	<i>P</i>	IDI		NRI	
			Estimated value (95% CI)	<i>P</i>	Estimated value (95% CI)	<i>P</i>
RCRI	0.693 (0.539–0.846)	0.011	-	-	-	-
RCRI + hs-cTnI, max	0.792 (0.669–0.915)	<0.001	0.041 (–0.004–0.118)	0.080	0.381 (–0.088–0.623)	0.173
RCRI + sST2	0.782 (0.665–0.899)	<0.001	0.04 (0.006–0.128)	0.007	0.285 (0.021–0.495)	0.020
RCRI + sST2 + hs-cTnI, max	0.843 (0.756–0.930)	<0.001	0.061 (0.017–0.134)	<0.001	0.366 (0.020–0.555)	0.033

Abbreviations: RCRI, revised Goldman cardiac risk index; hs-cTnI, high-sensitivity cardiac troponin I; sST2, soluble suppression of tumorigenicity-2; IDI, integrated discrimination improvement; NRI, net reclassification improvement; AUC, area under the curve; CI, confidence interval.

that the optimal cut-off values of hs-cTnI and sST2 for prediction of 30-day MACE were 53.0 ng/L and 182.5 ng/mL, respectively. hs-cTnI (max) and sST2 (max) showed fair predictive ability for 30-day MACE (AUC=0.780 and 0.725, respectively) compared with the poor predictive ability of RCRI score (AUC=0.693); however, there was no statistical difference between the AUCs (Fig. 1). Combination of hs-cTnI (max) and sST2 (max) predicted 30-day MACE better than RCRI score (AUC, 0.807 vs 0.693); combination of RCRI, hs-cTnI (max), and sST2 (max) showed the highest AUC (0.843). The poor predictive ability of RCRI score improved to good predictive ability, although there was no statistical difference between the AUCs.

A combined approach using below/above cut-off values of hs-cTnI and sST2 demonstrated differences in terms of predicting 30-day MACE ($P<0.001$). The proportion of 30-day MACE demonstrated a stepwise increase: 1.3% in group 0; 8.1% in group 1; and 30.3% in group 2 (Fig. 2A). Interestingly, this difference was also observed in 148 patients with an RCRI score of 0 or 1 ($P<0.001$) (Fig. 2B). Reclassification analyses demonstrated that addition of hs-cTnI and sST2 on top of RCRI score increased the prediction of 30-day MACE compared with RCRI score alone (Table 4).

DISCUSSION

The novelty of this study is that combined analysis of hs-cTnI and sST2 was performed in non-cardiac surgery patients to predict 30-day MACE. hs-cTnI and sST2 concentrations constituted independent predictors of 30-day MACE in patients admitted to the SICU following non-cardiac surgery; the optimal cut-off values of hs-cTnI and sST2 were 53.0 ng/L and 182.5 ng/mL, respectively (Table 3 and Fig. 1). sST2 is produced by both cardiac fibroblasts and cardiomyocytes in response to injury or stress, but non-myocardial production also occurs [23]; its prognostic utility has been observed in various clinical scenarios [14, 16, 19]. Of note, the present study has added another clinical sce-

nario that could be predicted by sST2 measurement.

In contrast to most previous studies that used conventional cardiac troponin assays [9, 11, 24, 25], we used the hs-cTnI assay [26]. Until date, there is no generally accepted optimal cut-off value for post-operative hs-cTnI concentrations either for MINS diagnosis or for prognosis prediction of 30-day MACE. Based on our data, a peak hs-cTnI concentration of 53.0 ng/L could be used as an optimal cut-off value to predict 30-day MACE.

The incidence of adverse outcomes related to non-cardiac surgery depends on the baseline risk. Among unselective patients older than 40 years, perioperative cardiac events were reported in 2.5% of cases [27]; using the RCRI model, in-hospital mortality increased from 1.4 to 7.4% [28]. Monitoring biomarkers could uncover silent ischemia identifying MINS in approximately 8% of patients, at least 45 years old, undergoing non-cardiac surgery [9]. The age of the enrolled patients in the present study was similar to that study; however, our study population was more selective, including only patients admitted to the SICU following major non-cardiac surgery and is thus predicted to have a higher incidence of adverse outcomes [9].

Utilization of perioperative biomarkers has been evolving in order to improve risk stratification in patients undergoing non-cardiac surgery. According to the 2014 European Society of Cardiology guidelines, cardiac troponins (T and I) should be considered in high-risk patients, both prior to and 48–72 hours post major surgery, in addition to N-terminal pro B-type natriuretic peptide (NT-proBNP) and BNP (Class IIb) [19]. Thus far, both troponin and natriuretic peptide assays have been chosen based on different mechanisms of ischemic injury and endocrine cardiac response to stress. Troponin T values of at least 0.02 ng/mL have been reported in 11.6% of patients with overnight admission and were associated with higher 30-day mortality [11]; preoperative NT-proBNP ≥ 725 pg/mL has been associated with a 4.8-fold relative risk of adverse outcomes in patients over 50 years of age with emergent non-cardiac surgery [29]. Postoperative surveillance has been emphasized in addition to preopera-

tive basal state, because it indicates ongoing cardiac ischemia or whole neuroendocrine responses related to surgical stress [9, 11, 24]. Despite these supporting studies [9, 11, 24, 28, 30], perioperative routine biomarker testing is not generally recommended (Class III) [6]. The present study suggests that a biomarker approach using hs-cTnI and sST2 may aid in prognosis prediction in patients following non-cardiac surgery. Our results are novel with respect to the combined use of a biomarker approach and clinical assessment using RCRI score; adding biomarkers to RCRI score improved the prediction of 30-day MACE compared with clinical assessment alone (Fig. 2 and Table 4). sST2 is increased by systemic inflammation, which is a prominent element following non-cardiac surgery, whereas hs-cTnI is specific for cardiac damage; therefore, the two biomarkers reflect different disease mechanisms, and it is possible that their prognostic value is additive.

This study has several limitations. First, we measured the serial changes of biomarkers from D0 to D3, without measuring the preoperative basal levels of the biomarkers. Further elucidation of the changes in biomarker levels would have been possible by measuring basal levels. Second, the blood samples were collected every morning, according to routine practice in the SICU, without maintaining a strict 24-hour interval for blood sampling. Third, a fundamental concern is how to interpret and manage the elevated biomarkers during the 72-hour postoperative period. Morning sampling is routine in clinical practice, and this type of monitoring (over 72 hours) may be sufficient to capture peak levels; thus, we could provide fundamental data regarding serial changes in hs-cTnI and sST2 postoperatively. However, the median time-to-first MACE was three days (ranged from D1 to D22) postoperatively during ongoing biomarker sampling; this would limit the clinical utility of biomarker assessment for prognostic stratification. This single-center study involving a limited study population should be further validated by additional studies in order to obtain a better understanding of the detailed implications of biomarker guidance for postoperative patient management following major non-cardiac surgery.

In conclusion, this study demonstrated the prognostic role of hs-cTnI and sST2 in predicting 30-day MACE in patients admitted to the SICU following major non-cardiac surgery. The cardiac biomarker approach combining hs-cTnI and sST2 showed superior prognostic performance compared with clinical assessment using RCRI score, and addition of biomarkers to clinical assessment further improved prognostic efficacy. The cardiac biomarker approach could constitute an objective and reliable tool for prognosis prediction in patients undergoing major non-

cardiac surgery.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this study are reported.

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