Preoperative NT-proBNP and CRP Predict Perioperative Major Cardiovascular Events in Noncardiac Surgery

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Running title: NT-proBNP and CRP predict perioperative event

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Abstract

Objective: To investigate whether simple and non-invasive measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) and/or C-reactive protein (CRP) can predict perioperative major cardiovascular event (PMCE).

Design: Prospective, single center, cohort study.

Setting: A 1900-bed tertiary-care university hospital in Seoul, Korea

Design and Patients: The predictive power of NT-proBNP, CRP, and Revised Cardiac Risk Index (RCRI) for the risk of PMCE (myocardial infarction, pulmonary edema, or cardiovascular death) were evaluated from a prospective cohort of 2054 elective major noncardiac surgery patients. Optimal cut-off values were derived from receiver operating characteristic curve (ROC) analysis.

Main outcome measurement: PMCE (myocardial infarction, pulmonary edema, or cardiovascular death) within postoperative 30 days.

Results: PMCE developed in a total of 290 patients (14.1%). Each increasing quartile of NT-proBNP or CRP level was associated with a greater risk of PMCE after adjustment for traditional clinical risk factors. The relative risk (RR) of highest versus lowest quartile was 5.2 for NT-proBNP (p<0.001) and 3.7 for CRP (p<0.001). Both NT-proBNP (cut-off = 301 ng/L) and CRP (cut-off = 3.4 mg/L) predicted PMCE better than RCRI (cut-off = 2) by ROC analysis (p<0.001). Moreover, the predictive power of RCRI (adjusted RR = 1.5) could be improved significantly by addition of CRP and NT-proBNP to RCRI (adjusted RR = 4.6) (p<0.001).

Conclusions: High preoperative NT-proBNP or CRP is a strong and independent predictor of perioperative major cardiovascular event in non-cardiac surgery. The predictive power of current clinical risk evaluation system would be strengthened by these biomarkers.

Keywords: perioperative cardiovascular event, natriuretic peptides, CRP
Perioperative major cardiovascular events (PMCE) such as acute myocardial infarction, pulmonary edema, or primary cardiovascular death are important causes of morbidity in patients undergoing a major noncardiac surgery. A number of clinical risk indices using scoring system have been developed, but the predictive power is still insufficient. Moreover, the results of preoperative myocardial stress test were not consistently predictive of risk. A simple and strongly predictive non-invasive test is clinically warranted.

We hypothesized that the pathophysiology of cardiovascular disease including inflammation, myocardial ischemia, or increased ventricular filling pressures would be important in the development of PMCE. Then cardiovascular biomarkers reflecting this pathophysiology would be useful for the prediction of perioperative risk. Based on abundant clinical data, practical availability, and background pathophysiology, we reasoned that N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP), representative biomarkers of hemodynamic stress and inflammation, respectively, would be predictive of PMCE. We investigated the predictive power of preoperative NT-proBNP and CRP and compared it with a well-validated clinical risk index for perioperative cardiovascular risk in a large prospective cohort of patients undergoing elective major non-cardiac surgery.
Methods

Patients

We enrolled patients who were referred to consulting cardiology physician for the evaluation of preoperative cardiovascular risk if the following criteria were fulfilled: 1) candidates for elective major non-cardiac surgery and aged more than 21 years old, and 2) at least one of cardiovascular risk factors such as hypertension, diabetes, angina, history of revascularization, heart failure, or stroke, or 3) abnormal preoperative electrocardiography with pathological Q wave or non-sinus rhythm. Major non-cardiac surgery was defined by procedures performed in the operating room requiring general, spinal, or epidural anesthesia, after exclusion of very low risk surgeries such as dermatologic, ophthalmologic, nasal, or auditory procedures.

We prospectively enrolled 2304 consecutive patients from November 2004 to April 2008. The following patients were excluded; surgery was not done within 2 weeks (N=118), significant myocardial ischemia or who required open heart surgery (N=29). To avoid bias in the NT-proBNP results from renal insufficiency, 103 patients with preoperative serum creatinine ≥2.0 mg/dL (≥176.8 μmol/L) were also excluded. The remaining 2054 patients had undergone non-cardiac surgery within 2 weeks and constituted the study cohort (Figure 1).

Data collection

Clinical perioperative cardiovascular risk was assessed according to the Revised Cardiac Risk Index (RCRI) modified by Lee, a well-validated and widely used risk prediction index. Briefly, RCRI calculates perioperative risk by sum of points. Each risk factor, including high-risk surgical procedures, history of ischemic heart disease, pulmonary edema, cerebrovascular disease, insulin-dependent diabetes, and serum creatinine > 2.0 mg/dL, is assigned one point. The risk of major cardiac event including myocardial infarction, pulmonary edema, primary cardiac arrest and complete heart block predicted by RCRI was known to be 0.4% to 11% according to RCRI score of 0 to ≥ 3.

Patient's clinical history and functional capacity were evaluated according to the
ACC/AHA guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. Basic laboratory tests including electrocardiography, chest X-ray, NT-proBNP, and CRP were evaluated within 2 weeks before surgery. Additional non-invasive tests were performed by physician’s discretion. Electrocardiography and serum troponin I were evaluated at the end of the day of surgery and 24 hours later. Chest X-ray was taken on the next day. Any abnormal signs or symptoms suggesting pulmonary edema or myocardial ischemia was followed by meticulous evaluation of perioperative cardiac status with repeated cardiac serum markers and electrocardiography. If active pulmonary edema or ongoing myocardial ischemia was found, the patient was transferred to the cardiovascular team and treated appropriately. Patients were followed up by the consulting physician until discharge or up to 30 days in-hospital after surgery. In case of mortality, the cause of death was decided on the consensus of the surgeon, anaesthesiologist, and cardiovascular consulting physician.

Primary endpoint was perioperative major cardiovascular event (PMCE), which was defined by any single or combined event of secondary endpoints including myocardial infarction, development of pulmonary edema, or primary cardiovascular death. Myocardial infarction was defined by a rise in postoperative troponin I above the 99th percentile of upper reference limit (0.78 ng/mL, Roche Diagnostics, Switzerland). Diagnosis of pulmonary edema required a formal reading of chest X-ray by a radiologist consistent with the complication. Primary cardiovascular death was defined by sudden death that could not be explained by any other non-cardiovascular postoperative complications. All clinical events were collected by a research nurse and investigated by physicians. This study protocol was approved by the institutional review board of Samsung Medical Center.

Statistics
Perioperative risk predictors (RCRI, CRP, and NT-proBNP) were treated as continuous variables or ordered categorical variables. Logarithmically transformed values of NT-proBNP and CRP were also used to minimize distribution skewness and kurtosis. Dose-response relationship between risk predictors and clinical outcome were investigated by Jonckheere-Terpstra test for trend. The predictive power of each risk predictor was also quantitatively evaluated with relative risk per 1-SD increase of RCRI and logarithmically transformed biomarker levels. Receiver-operating characteristic (ROC)
analysis was performed to calculate sensitivity, specificity, area under the curve, and the optimal cut-off. The predictive power of each method was compared using Hanley and McNail method. Relative risk was calculated by Zhang and Yu’s method. Relative risk was also calculated for the risk predictors with values categorized by optimal cut-off levels, or combination of these cut-off levels in an additive manner. Independent predictors of PMCE in univariate analysis were included in multivariate logistic models with forward conditional methods. A p value < 0.05 (2-sided) was considered significant. SPSS version 13.0 was used mostly. ROC curves were compared using Medcalc version 9.6.
Results

Clinical characteristics
Preoperative clinical characteristics of the study population are shown in Table 1. Briefly, most patients had good functional status without overt heart failure (functional class I or II in 94.6% and no heart failure in 97.0%). A history of angina was found in 13.2%, including 8.0% of myocardial infarction. Percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) had been performed before non-cardiac surgery in 14.8%. Two-dimensional echocardiography was performed in most patients (93.6%), revealing abnormal left ventricular wall motion in 19.9% of patients. Evidence of myocardial ischemia which was defined by positive non-invasive test or significant coronary artery stenosis was found in 21.6%. Preoperative beta-blocker or statin was used in 17.3% and 14.8%, respectively.

Perioperative clinical evaluation
Most patients received general anesthesia (97.1%). Ninety-three patients (4.5%) underwent urgent surgery within 24 hours after consultation because of altered clinical situation. These cases were not excluded from the analysis (Table 2).

Clinical outcomes
Perioperative major cardiovascular event (PMCE) had developed in 290 (14.1%) patients. Individual patients may have had more than one event, and all events were counted as an incidence. There were 102 (5.0%) acute myocardial infarction, 248 (12.1%) pulmonary edema, and 20 (1.0%) deaths, which were similar to previous studies evaluated patients with risk of cardiovascular disease.¹ Five patients died due to postoperative disease progression or surgical complication (0.2%), and 15 deaths were determined to be primary cardiovascular death (0.7%), which included 3 (0.2%) acute myocardial infarction, 2 (0.1%) stress induced cardiomyopathy,¹⁷ 4 (0.2%) aortic aneurysm rupture or dissection, 1 (0.1%) stroke, and 5 (0.2%) sudden death of unknown cause (Figure 1) (Table 3).

Predictive power of perioperative risk predictors
We evaluated the continuous values of three risk predictors against perioperative events. Not only increasing score of a clinical predictor, RCRI, but also increasing quartile of
biomarker levels, NT-proBNP and CRP, was associated with a greater risk of PMCE (p<0.001) (Figure 2).

Next we investigated whether the risk predictors are related to clinical outcomes independently each other. Each 1-SD increase in RCRI (1 to 2) (adjusted relative risk (RR) = 1.26 [95% CI = 1.10–1.44]), log CRP (2.7 to 15.1 mg/L) (1.74 [1.55–1.95]), or log NT-proBNP (135 to 601 ng/L) (2.17 [1.91–2.45]) was associated with 1.3- to 2.2-fold increased rate of PMCE, even after adjustment for other risk predictors and traditional clinical risk factors. By subgroup analysis, CRP and NT-proBNP were also significantly associated with all secondary endpoints, whereas RCRI was not associated with AMI or primary cardiovascular death. Each 1-SD increase in log CRP or log NT-proBNP was also associated with 1.6- to 2.3-fold increased risk of PMCE (Table 4).

Augmentation of predictive power of clinical risk index by addition of biomarkers

Risk predictors categorized by optimal cut-off levels were used to test whether the predictive power could be increased by the combination of multiple risk factors. RCRI cut-off (≥2) was associated with 1.5-fold increased risk of PMCE after adjustment for age, sex, and traditional clinical risk factors (adjusted RR = 1.50 [95% CI =1.17–1.91]). The risk of PMCE based on CRP cut-off (≥3.4 mg/L) and NT-proBNP cut-off (≥301 ng/L) were much higher, 2.7-fold and 3.9-fold, respectively (CRP cut-off, 2.75 [2.16–3.45]; NT-proBNP cut-off, 3.89 [3.15–4.14]) (Table 4). Higher CRP and NT-proBNP values were also associated with 2.5- to 5.4-fold increased risk of secondary endpoints including AMI, pulmonary edema, and primary cardiovascular death (p<0.05), whereas higher RCRI was not associated with AMI or primary cardiovascular death (Table 4).

The addition of biomarkers to RCRI increased the relative risk of RCRI for clinical events 3-fold. For PMCE, the adjusted RR of RCRI increased from 1.50 [95% CI = 1.17–1.91] to 4.55 [3.69–5.52] after addition of CRP and NT-proBNP. The relative risks for secondary endpoints including AMI, pulmonary edema, and primary cardiovascular death also increased 3- to 7-fold (Table 4). The increase of predictive power of RCRI by addition of biomarkers to RCRI was again calculated using ROC analysis. For PMCE, AUC (area under curve) of combination of RCRI cut-off (≥2) and NT-proBNP cut-off
(≥301 ng/L), 0.735 [0.714–0.754], and AUC of combination of RCRI cut-off and CRP cut-off (≥3.4 mg/L), 0.694 [0.673–0.715], were significantly higher than AUC of RCRI cut-off, 0.592 [0.570–0.615], (p<0.001, each). AUC of combination of RCRI cut-off and NT-proBNP cut-off and CRP cut-off, 0.772 [0.752–0.790], was even much higher than AUC of RCRI cut-off (p<0.001) (Figure 3 panel A). The increase in AUC by addition of biomarker cut-offs to RCRI cut-off was also evident in all secondary endpoints including AMI, pulmonary edema, and primary cardiovascular death (Figure 3 panel B-D).
Discussion

Our study showed that the predictive power of a current perioperative clinical risk index could be strengthened significantly by the simple addition of cardiovascular biomarkers, NT-proBNP and CRP. Our findings can be summarized that the average sensitivity of predicting perioperative major cardiovascular event increased from 59% to 77% after addition of biomarkers to clinical risk prediction system.

Predictive power of biomarker versus clinical risk index

The Revised Cardiac Risk Index modified by Lee (RCRI), which has been shown to be superior to other perioperative risk indices was selected as the clinical risk predictor in our study. The results showed that a single cardiovascular biomarker, NT-proBNP or CRP, is superior to clinical risk indices for the prediction of perioperative events. In addition, both NT-proBNP and CRP were significantly associated not only with all clinical events but also with all subsidiary events including AMI, pulmonary edema, and primary cardiovascular death, whereas RCRI was not associated with primary cardiovascular death. Furthermore, NT-proBNP and CRP were not only useful for risk prediction but also shown to improve the predictive power of clinical risk index. The addition of NT-proBNP and CRP to the clinical risk index increased the adjusted relative risk 3-fold.

Role of NT-proBNP and CRP in the pathophysiology of perioperative cardiovascular events

The pathophysiology of perioperative myocardial infarction has been explained by responses to perioperative surgical stress represented by a catecholamine surge with associated hemodynamic stress, systemic inflammation, and hypercoagulability. High NT-proBNP was associated not only with a high risk of pulmonary edema but also with AMI and primary cardiovascular death in our study. This could be explained by the release of NT-proBNP or B-natriuretic peptide (BNP) from subclinical ischemic or injured myocardial tissue regardless of hemodynamic stress. Our results strongly suggest that NT-proBNP could be marker of myocardial ischemia or generalized cardiac impairment in perioperative situations as well as non-surgical situations. The predictive power of CRP was also better than the clinical risk index in this study. However the high CRP levels did not predict clinical events beyond NT-proBNP. Previous population
based studies showed that the value of CRP in cardiovascular risk prediction was moderate or less than traditional risk factors.\textsuperscript{21,22} A recently published study showed that NT-proBNP was better than CRP for the prediction of sudden cardiac death.\textsuperscript{23} Relatively high CRP level in perioperative condition might lead to greater contribution of CRP for the risk prediction in our study.

**Limitations**
This study was performed at single center. Only patients who had undergone formal preoperative cardiovascular consultation were included. However, given the strength of our results and wide variability in the predictive power of risk indices which highly depend on study population, it is unlikely that enrollment of more patients would have changed the main results of our study.\textsuperscript{1} Long-term follow-up after discharge was not performed, although most postoperative cardiovascular events is known to develop in early postoperative periods.\textsuperscript{24,25} Exclusion of patients with renal dysfunction might have affected the predictive power of RCRI, which includes renal function evaluation.\textsuperscript{13,26} Therefore, our results cannot be generalized to patients with renal dysfunction. The presence of preoperative infection or the use of antibiotics, which might affect the level of CRP or the severity of perioperative systemic inflammation, was not used as an exclusion criterion. The relationship between infection and perioperative cardiovascular disease is little known and requires further investigation. The use of preoperative beta-blocker or statin was less than 20\% and was not associated with clinical events in our study. The benefit of beta-blocker or statin is currently in debate even in high risk patients, and large prospective trials are needed to confirm it.\textsuperscript{6,27,28}

In conclusion, our results demonstrate that high preoperative NT-proBNP and CRP levels are strong and independent predictors of perioperative cardiovascular event following non-cardiac surgery. Furthermore, the predictive power of the current clinical perioperative risk index could be strengthened significantly by the addition of these biomarkers. Evaluation of preoperative NT-proBNP and CRP is a practical, simple, and reasonable strategy to improve perioperative risk prediction strategies with minimal clinical burden and cost.

**Funding**
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Research Development Program and the In-Sung Foundation for Medical Research, Seoul, Korea.

Conflict of interest: None declared.
References


21. van der Meer IM, de Maat MP, Kiliaan AJ, et al. The value of C-reactive protein


## Tables

### Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Frequency (%) or median with interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 (61 – 73)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1247 (60.7)</td>
</tr>
<tr>
<td>Functional class III or IV</td>
<td>112 (5.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>355 (17.3)</td>
</tr>
<tr>
<td>Diabetes treated with insulin</td>
<td>71 (3.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1247 (60.7)</td>
</tr>
<tr>
<td>Previous or current heart failure</td>
<td>62 (3.0)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>188 (9.3)</td>
</tr>
<tr>
<td>Angina</td>
<td>270 (13.2)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>165 (8.0)</td>
</tr>
<tr>
<td>Previous revascularization*</td>
<td>304 (14.8)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 (0.7 – 1.1)</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>109.3 (47.0 – 352.8)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>2.0 (0.7 – 8.0)</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>2054 (100)</td>
</tr>
<tr>
<td>Pathological Q waves</td>
<td>111 (5.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>164 (8.0)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>14 (0.7)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>1923 (93.6)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≤40%</td>
<td>95 (4.6)</td>
</tr>
<tr>
<td>Abnormal left ventricular wall motion</td>
<td>408 (19.9)</td>
</tr>
<tr>
<td>Preoperative noninvasive test†</td>
<td>765 (37.2)</td>
</tr>
<tr>
<td>Overall positive result for ischemia</td>
<td>188 (9.2)</td>
</tr>
<tr>
<td>Preoperative Invasive test</td>
<td>544 (26.5)</td>
</tr>
<tr>
<td>Significant coronary artery disease by invasive test</td>
<td>359 (17.5)</td>
</tr>
<tr>
<td>Any evidence of myocardial ischemia§</td>
<td>444 (21.6)</td>
</tr>
</tbody>
</table>

Data are shown as frequency (%) or median with interquartile range, as appropriately.

*Previous revascularization includes percutaneous coronary intervention in 222 cases and bypass surgery in 82 cases.
†Preoperative noninvasive test includes SPECT in 577 cases, Treadmill test in 113 cases, and stress echocardiography in 47 cases.
§Positive non-invasive test or coronary artery stenosis of more than 50% was defined as any evidence of myocardial ischemia.
Table 2. Surgical Procedure and Perioperative Risk

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular surgery</td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>160 (7.8)</td>
</tr>
<tr>
<td>Suprainguinal vascular</td>
<td>98 (4.8)</td>
</tr>
<tr>
<td>Infrainguinal vascular</td>
<td>158 (7.7)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>97 (4.7)</td>
</tr>
<tr>
<td>Other vascular</td>
<td>18 (0.9)</td>
</tr>
<tr>
<td>Non-vascular surgery</td>
<td></td>
</tr>
<tr>
<td>Thorax</td>
<td>85 (4.1)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>501 (24.4)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>178 (8.7)</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>439 (21.4)</td>
</tr>
<tr>
<td>Prostate</td>
<td>82 (4.0)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>55 (2.7)</td>
</tr>
<tr>
<td>Other surgery</td>
<td>182 (8.9)</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>1994 (97.1)</td>
</tr>
<tr>
<td>Urgent surgery</td>
<td>93 (4.5)</td>
</tr>
<tr>
<td>RCRI (median, interquartile range)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>RCRI = 0</td>
<td>555 (27.0)</td>
</tr>
<tr>
<td>RCRI = 1</td>
<td>846 (41.2)</td>
</tr>
<tr>
<td>RCRI = 2</td>
<td>579 (28.2)</td>
</tr>
<tr>
<td>RCRI = 3</td>
<td>69 (3.4)</td>
</tr>
<tr>
<td>RCRI = 4</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>High risk surgery by RCRI*</td>
<td>844 (41.1)</td>
</tr>
</tbody>
</table>

Data are shown as frequency (percent).

*Defined by intraperitoneal, intrathoracic, or suprainguinal vascular surgery according to RCRI (Revised Cardiac Risk Index modified by Lee).
## Table 3. Clinical Outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative major cardiovascular event (PMCE)</td>
<td>290 (14.1)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>102 (5.0)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>26 (1.3)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>24 (1.2)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>New or aggravated heart failure</td>
<td>248 (12.1)</td>
</tr>
<tr>
<td>Primary cardiovascular death*</td>
<td>15 (0.7)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Stress induced cardiomyopathy</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Aortic disease</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Death due to postoperative complication or disease progression</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>All death</td>
<td>20 (1.0)</td>
</tr>
</tbody>
</table>

Data are shown as frequency (percent).

*Death that was not caused by postoperative complication or underlying non-cardiovascular disease progression.
Table 4. Clinical Outcomes According to the Risk Predictors

<table>
<thead>
<tr>
<th></th>
<th>PMCE</th>
<th>AMI</th>
<th>PE</th>
<th>CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>p</td>
<td>RR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Per 1-SD increase*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCRI</td>
<td>1.26 (1.10-1.44)</td>
<td>0.001</td>
<td>1.18 (0.88-1.56)</td>
<td>0.27</td>
</tr>
<tr>
<td>CRP</td>
<td>1.74 (1.55-1.95)</td>
<td>&lt;0.001</td>
<td>1.58 (1.28-1.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2.17 (1.91-2.45)</td>
<td>&lt;0.001</td>
<td>1.55 (1.28-1.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optimal cut-off of each risk predictors†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCRI</td>
<td>1.50 (1.17-1.91)</td>
<td>0.002</td>
<td>1.14 (0.70-1.86)</td>
<td>0.59</td>
</tr>
<tr>
<td>CRP</td>
<td>2.75 (2.16-3.45)</td>
<td>&lt;0.001</td>
<td>2.62 (1.66-4.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>3.89 (3.15-4.74)</td>
<td>&lt;0.001</td>
<td>2.54 (1.68-3.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combination of best cutoff of each predictors§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCRI or CRP or NT-proBNP≥ cutoff§</td>
<td>4.55 (3.69-5.52)</td>
<td>&lt;0.001</td>
<td>3.24 (2.10-4.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Investigate independent association of each risk predictors with clinical outcomes were shown as adjusted relative risk (RR) with 95% confidence intervals (CI), all three risk predictors were included in the logistic regression analysis with forward conditional method. Analysis was adjusted with all significant univariate risk factors including age and sex. PMCE, perioperative major cardiovascular event; AMI, acute myocardial infarction; PE, pulmonary edema; CV Death, primary cardiovascular death.

*Measured in linear values, 1-SD increase from mean corresponded to 1 to 2 for RCRI, 135 ng/L to 601 ng/L for NT-proBNP, and 2.7 mg/L to 15.1 mg/L for CRP, respectively.
†Optimal cut-off values were ≥2 for RCRI, ≥301 ng/L for NT-proBNP, and ≥3.4 mg/L for CRP.
§Defined by at least two of three risk predictors are higher than cutoff values.
Figure Legends

Figure 1. Study flowchart

Figure 2. Clinical outcomes according to the risk predictors
PMCE, perioperative major cardiovascular event; AMI, acute myocardial infarction; PE, pulmonary edema; CV death, primary cardiovascular death. * p<0.001 by Jonckheere-Terpstra test for trend.

Figure 3. ROC analysis of perioperative risk predictors
The predictive power of each combination of categorized risk predictor in an additive manner was investigated. Risk predictors were categorized according to the optimal cut-off levels derived from ROC analysis, which were 2 for RCRI, 301 ng/L for BNP, and 3.4 mg/L for CRP. AUCs with 95% CI are shown below each panel. *p<0.05 by Hanley and McNeil methods.

Panel A. ROC for PMCE. *p<0.001 for all, except RCRI + NT-proBNP versus RCRI + NT-proBNP + CRP (p=0.001), and RCRI + CRP versus RCRI + NT-proBNP (p=0.010).

Panel B. ROC for AMI. *p<0.001 for all, except RCRI + NT-proBNP versus RCRI + NT-proBNP + CRP (p=0.026), RCRI + CRP versus RCRI + NT-proBNP + CRP (p=0.002), and RCRI + CRP versus RCRI + NT-proBNP (p=0.590).

Panel C. ROC for pulmonary edema. *p<0.001 for all, except RCRI + CRP versus RCRI + NT-proBNP (p=0.004), and RCRI + NT-proBNP versus RCRI + NT-proBNP + CRP (p=0.001).

Panel D. ROC for primary cardiovascular death. *RCRI versus CRP, p=0.021; RCRI versus RCRI + NT-proBNP, p=0.012; RCRI versus RCRI + NT-proBNP + CRP, p=0.002; RCRI + CRP versus RCRI + NT-proBNP + CRP, p=0.021.
Candidates for elective major non-cardiac surgery were referred to consulting physician for the preoperative evaluation of cardiovascular risk (N=2304)

Surgery was cancelled or not done within 2 weeks (N=118)

Ongoing myocardial ischemia or open heart surgery (N=29)

Creatinine ≥ 2.0 mg/dL (N=103)

Enrolled for prospective registry (N=2054)

Perioperative major cardiovascular event (PMCE) occurred in 14.1% (N=291)

Acute myocardial infarction in 5.0% (N=102)

Pulmonary edema in 12.1% (N=248)

Primary cardiovascular death in 0.7% (N=15)
Figure 2. Clinical outcomes according to the risk predictors

A

PMCE

Event %

0 10 20 30 40

0 1 2 ≥3 1Q 2Q 3Q 4Q

RCRI score

NT-proBNP quartiles

CRP quartiles

*B

B

AMI

Event %

0 10 20 30 40

0 1 2 ≥3 1Q 2Q 3Q 4Q

RCRI score

NT-proBNP quartiles

CRP quartiles

*C

C

PE

Event %

0 10 20 30 40

0 1 2 ≥3 1Q 2Q 3Q 4Q

RCRI score

NT-proBNP quartiles

CRP quartiles

**

D

CV Death

Event %

0 1 2 3 4

0 1 2 3 4

RCRI score

NT-proBNP quartiles

CRP quartiles

***
Figure 3. ROC analysis of perioperative risk predictors

A. PMCE

- RCRI+NTproBNP+CRP: 0.772±0.017 [95% CI 0.752–0.790]
- RCRI+NTproBNP: 0.735±0.018 [95% CI 0.714–0.754]
- RCRI+CRP: 0.694±0.019 [95% CI 0.673–0.715]
- RCRI: 0.592±0.019 [95% CI 0.570–0.615]

B. AMI

- RCRI+NTproBNP+CRP: 0.761±0.029 [95% CI 0.741–0.780]
- RCRI+NTproBNP: 0.720±0.030 [95% CI 0.700–0.740]
- RCRI+CRP: 0.705±0.031 [95% CI 0.685–0.726]
- RCRI: 0.611±0.031 [95% CI 0.589–0.633]

C. PE

- RCRI+NTproBNP+CRP: 0.777±0.018 [95% CI 0.758–0.796]
- RCRI+NTproBNP: 0.738±0.019 [95% CI 0.718–0.758]
- RCRI+CRP: 0.689±0.020 [95% CI 0.668–0.710]
- RCRI: 0.582±0.020 [95% CI 0.560–0.604]

D. CV Death

- RCRI+NTproBNP+CRP: 0.737±0.077 [95% CI 0.717–0.757]
- RCRI+NTproBNP: 0.678±0.080 [95% CI 0.657–0.699]
- RCRI+CRP: 0.639±0.080 [95% CI 0.617–0.660]
- RCRI: 0.515±0.077 [95% CI 0.492–0.537]
Noncardiac Surgery

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