

# Clinical utility of the revised cardiac risk index in older Chinese patients with known coronary artery disease

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**Objectives:** The revised Cardiac Risk Index (RCRI) is the most widely used risk prediction tool for postoperative cardiac adverse events. We aim to explore the predictive ability of the RCRI in older Chinese patients with coronary artery disease (CAD) undergoing noncardiac surgery, which has not been previously evaluated.

**Methods:** We performed a multicenter, prospective study. We enrolled a total of 1,202 patients, aged >60 years, with a history of CAD who underwent noncardiac surgery. Perioperative data were extracted from an electronic database. The primary end point was defined as an occurrence of a postoperative major cardiac event (PoMCE) within 30 days. Logistic regression analysis was performed to evaluate the performance of the RCRI. A modified RCRI was created and compared with the original RCRI with regard to its ability to predict postoperative cardiac events.

**Results:** Of the enrolled patients, 4.3% experienced PoMCE. Most components of the RCRI were not predictive of postoperative cardiac events with the exception of insulin-dependent diabetes mellitus (odds ratio =2.38, 95% CI: 1.11–5.11;  $P=0.03$ ). The RCRI performed no better than chance (area under the curve =0.53; 95% CI: 0.45–0.61) in identifying patients' cardiac risk. The modified score had a higher discriminatory ability toward PoMCE (c index, 0.69 versus 0.53;  $P<0.01$ ).

**Conclusion:** The original RCRI shows poor predictive ability in Chinese patients with CAD undergoing noncardiac surgery.

**Keywords:** cardiovascular risk factors, older patient, coronary artery disease, risk prediction model

## Introduction

Globally, more than 300 million people undergo noncardiac surgery every year. Cardiac complications occur after at least 2% of elective noncardiac procedures and account for one-third of postoperative deaths.<sup>1</sup> Coronary artery disease (CAD) is a major health problem in China. Based on the data from the 2008 Fourth Family Health Survey, the overall prevalence of CAD was 7.7%. This finding indicated that there were more than 10 million subjects with CAD in Mainland China in 2008.<sup>2</sup> The prevalence of cardiovascular disease among the surgical population in China is expected to increase in the next decade. Therefore, effective preoperative risk stratification that implements readily available clinical information is required for prioritization of patients.

The revised cardiac risk index (RCRI), also known as the Lee index, was originally published in 1999, and has been used worldwide since this time.<sup>3</sup> The 2014 American College of Cardiology and American Heart Association Guideline recommends estimating the perioperative risk of adverse cardiac events with the RCRI.<sup>4</sup> However,

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the RCRI was originally developed for all patients undergoing major noncardiac surgery rather than cardiac patients. Furthermore, the medical treatment strategy toward CAD has greatly evolved since the development of the RCRI. The discriminatory ability of this index in modern patients with CAD may be compromised.

The goals of this study were 1) to validate the RCRI in a multicenter cohort of patients with CAD undergoing noncardiac surgery and 2) to determine whether modification of the current risk factors or adoption of other risk factors would improve upon discrimination of cardiac risk prediction compared with the original RCRI.

## Materials and methods

### Study population

We performed a multicenter, prospective study of consecutive patients who underwent noncardiac surgery between March 1, 2008, and February 28, 2010. We included patients from five university-affiliated tertiary care hospitals in China. The details of the original study have been described previously.<sup>5</sup> The local medical ethics committee of Peking Union Medical College Hospital approved this study. The original inclusion criterion was patients with a history of CAD undergoing intermediate-to high-risk noncardiac surgery based on the American College of Cardiology/American Heart Association guidelines. Original exclusion criteria included the following: 1) patients who underwent emergency surgery or low-risk surgery, 2) patients with American Society of Anesthesiologists classification of V or VI, and 3) patients with congenital heart disease or cardiomyopathy. For the present study, we further excluded patients with incomplete data that were necessary to extrapolate the RCRI. The primary outcome measure was the occurrence of a postoperative major cardiac event (PoMCE) within 30 days. PoMCEs were defined as cardiac death, nonfatal myocardial infarction, nonfatal cardiac arrest, and heart failure. All possible clinically relevant preoperative and intraoperative factors were extracted from the database and analyzed.

### Statistical analysis

De-identified data on demographics, preoperative risk factors, intraoperative variables, postoperative monitoring variables, and 30-day postoperative cardiac complications were retrieved from the database. The RCRI score was calculated for each patient in accordance with the original study. Each component of the RCRI was assigned a score of 0 or 1 (1 = yes, 0 = no). The six components of the RCRI were as follows: 1) history of ischemic heart disease, 2) history

of congestive heart failure, 3) history of cerebrovascular disease (stroke or transient ischemic attack), 4) history of diabetes requiring preoperative insulin use, 5) chronic kidney disease (creatinine levels >2 mg/dL), and 6) undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery. All data analyses were conducted independently by investigators who did not participate in the original study. Normally distributed continuous variables are expressed as mean  $\pm$  SD and were compared using the two-tailed Student's *t*-test. Categorical variables are expressed as frequency (%), and were compared using chi-square analysis. Univariate analyses were performed to select possible risk factors for major adverse cardiac event (MACE). Multivariate logistic regression analysis was used to evaluate the predictive ability of the original RCRI model. A modified RCRI (mRCRI) was established by incorporating easily accessible clinical data that can be obtained from the preoperative period. A forward stepwise logistic regression analysis was performed. Each variable was sequentially added to the original RCRI. Variables with a *P*-value <0.05 were maintained. The generated models were then compared using receiver operating characteristic (ROC) curves and area under the curve analysis. The parameters with optimal predictive scores and those that maintained the highest discriminative capacity of the new model were selected. A value of *P*<0.05 was considered as significant. Statistical analyses were performed using Stata/MP 14.0 version (StataCorp., College Station, TX, USA).

## Results

### Demographic data

From the original dataset of 1,422 patients, 220 were excluded because of incomplete data. Among the included 1,202 patients (age, 69.5 $\pm$ 5.3 years), 52 (4.3%) patients experienced PoMCE (Table 1). Baseline information analysis showed that age (>70 years), female sex, body mass index (BMI) <18 kg/m<sup>2</sup>, insulin-dependent diabetes mellitus, creatinine levels, incidence of intraoperative hypotension, and a long operation time were different between patients who did and those who did not experience PoMCE (Table 2).

### Calculation of the RCRI

Rates of major cardiac adverse events with an RCRI <2 and  $\geq$ 2 were 4.5% (n=314) and 4.2% (n=888), respectively (Table 3). The relationships of the six components included in the original RCRI model with PoMCE were evaluated by multivariate regression (Table 4). The modified model included six preoperative clinical factors, and each were allocated a score of 1 for the following: 1) history of myocardial

**Table 1** Number of patients with MACE (n=1,202)

PoMCE	N	Percentage
Cardiac death	6	0.5
Nonfatal myocardial infarction	29	2.4
Nonfatal cardiac arrest	1	0.1
Congestive heart failure	24	2.0

**Notes:** Eight patients experienced more than one PoMCE; cardiac death: any death, unless an unequivocal noncardiac cause could be established; nonfatal cardiac arrest: an absence of cardiac rhythm or presence of chaotic rhythm requiring any component of basic or advanced cardiac life support; nonfatal myocardial infarction: increase and gradual decrease in troponin level or a faster increase and decrease of creatine kinase isoenzyme as markers of myocardial necrosis in the company of at least one of the following: ischemic symptoms, abnormal Q waves on the ECG, ST-segment elevation or depression; or coronary artery intervention or a typical decrease in an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for the troponin elevation; congestive heart failure: new in-hospital signs or symptoms of dyspnea or fatigue, orthopnea, paroxysmal nocturnal dyspnea, increased jugular venous pressure, signs of cardiomegaly or pulmonary congestion.

**Abbreviations:** ECG, electrocardiography; MACE, major adverse cardiac event; PoMCE, postoperative major cardiac event.

infarction, 2) female sex, 3) insulin-dependent diabetes mellitus, 4) BMI <18 kg/m<sup>2</sup>, 5) age >70 years, and 6) atrial fibrillation. Another risk model involving a seventh intraoperative parameter (intraoperative hypotension) with a score of 1 was also investigated. Rates of PoMCE of different risk stratification methods are shown in Table 3. A high RCRI was not correlated with the incidence of PoMCE, while mRCRI and mRCRI+hypo were strongly correlated with the occurrence of PoMCE. An mRCRI ≥3 was associated with a tripled risk of PoMCE compared with an mRCRI <3 (odds ratio [OR]=3.10, 95% CI 1.64–5.90, *P*<0.01). Patients with an mRCRI+hypo ≥3 were 3.6 times more likely to develop PoMCE compared with patients with an mRCRI+hypo <3 (OR=3.63, 95% CI 2.06–6.41, *P*<0.01). ROC analysis was carried out for all three models. The RCRI had a poor discriminatory ability (ROC area 0.532, 95% CI 0.452–0.612), while the mRCRI showed significantly improved ability (ROC area 0.689, 95% CI 0.6210..757, *P*<0.05) to predict PoMCE within 30 days postoperatively. When the variable of intraoperative hypotension was added to stratify patients, the prognostic accuracy measured as the C statistic rose from 0.689 to 0.760 (*P*>0.05; Figure 1).

## Discussion

Myocardial injury after noncardiac surgery is associated with a marked increase in 30-day mortality, longer hospitalization, and increased health care costs.<sup>6</sup> The previously reported incidence of postoperative cardiac complications in cardiac patients ranged from 3.9% to 10%.<sup>7–9</sup> Patients with known ischemic heart disease are traditionally thought to have a higher cardiac risk. In our study, the incidence of PoMCE

**Table 2** Univariate analyses of preoperative risk factors of PoMCE

Variable	Patients without PoMCE (n=1,150)	Patients with PoMCE (n=52)	P-value
<b>Demographic</b>			
Age (years)	69.35±6.26	71.8±6.61	0.01
Sex = male	607 (53.9)	15 (36.1)	0.03
Education*	239 (21.2)	7 (17)	0.52
BMI (kg/m <sup>2</sup> ), mean ± SD	24.45±3.57	23.98±3.72	0.41
BMI <18 (kg/m <sup>2</sup> )	36 (3.1)	6 (11.5)	<0.01
BMI >30 (kg/m <sup>2</sup> )	60 (5.2)	3 (5.8)	0.86
NYHA = I	245 (22)	4 (9.7)	0.17
=2	743 (66)	32 (78)	
=3	135 (11.0)	5 (12.2)	
<b>RCRI component</b>			
History of ischemic heart disease	1,150 (100)	52 (100)	NA
History of congestive heart failure	20 (1.7)	3 (5.7)	0.27
History of cerebrovascular disease	126 (11.2)	4 (9.7)	0.77
Diabetes requiring insulin	101 (8.8)	11 (21.2)	<0.01
High-risk surgery*	774 (67.3)	32 (61.5)	0.39
<b>Clinical risk</b>			
Hypertension	645 (56.1)	35 (65.8)	0.22
Diabetes mellitus	249 (21.7)	16 (29.3)	0.12
Atrial fibrillation	32 (2.8)	6 (11.5)	<0.01
Angina	265 (22.5)	19 (34.1)	0.08
COPD	87 (7.2)	7 (17)	0.12
Asthma	24 (0.21)	2 (3.8)	0.39
<b>Surgery</b>			
Vascular surgery	30 (2.5)	1 (1.9)	0.02
Intrathoracic surgery	186 (16.1)	3 (5.8)	
Intra-abdominal surgery	558 (48.5)	28 (55.7)	
Orthopedic surgery	192 (16.7)	8 (15.4)	
Head and neck surgery	111 (9.6)	6 (11.5)	
Neurosurgery	36 (3.1)	5 (9.6)	
<b>Laboratory test and imaging</b>			
Hemoglobin level (g/dL), mean ± SD	128.4±21.0	121.7±29.0	0.05
Creatinine (μmol/L), mean ± SD	77.1±23.9	86.1±30.2	0.02
<b>Revascularization</b>			
CABG	26 (2.2)	0	0.325
PCI	106 (9.2)	6 (11.5)	0.573
<b>Intraoperative parameters</b>			
Intraoperative hypotension	307 (26.7)	30 (57.7)	<0.01
Intraoperative hypoxemia	14 (1.2)	1 (1.9)	0.48
Optime >2.5 h	460 (42.6)	29 (55.8)	0.02

**Notes:** Data presented as n (%) unless otherwise specified. \*High risk surgery defined as suprainguinal vascular, intraperitoneal, or intrathoracic surgery.

**Abbreviations:** BMI, body mass index; CABG, coronary artery bypass grafting; NA, not applicable; NYHA, New York Heart Association Functional status; Optime, operation time; PCI, percutaneous coronary intervention; PoMCE, postoperative major cardiac event; RCRI, revised cardiac risk index.

tended to fall in the lower range of previously reported data, despite the older age of the enrolled population. This finding is in accordance with earlier detection and more prompt intervention of CAD compared with a decade ago. Results from our study agree with previous findings that the presence

**Table 3** Risk stratification by original and modified RCRI

Prediction model	0	1	2	3	4	5	OR (CI)	P-value
RCRI	0	4.5 (14/314)	3.6 (27/715)	5.9 (9/152)	15.8 (3/19)	0 (0/2)	1.29 (0.87–1.92)	0.20
mRCRI	2.4 (6/250)	3.0 (14/461)	5.1 (18/355)	11 (13/118)	5.5 (1/18)	0	1.64 (1.24–2.16)	<0.01
mRCRI + hypo	0.93 (1/185)	1.39 (8/196)	3.90 (20/392)	11.17 (16/171)	8.57 (7/54)	100 (4/4)	1.96 (1.52–2.52)	<0.01

**Abbreviations:** mRCRI, modified RCRI; OR, odds ratio; RCRI, revised cardiac risk index.

of a history of CAD, transient ischemic attack, and diabetes does not predict mortality for patients undergoing noncardiac surgery.<sup>6</sup> However, once combined with other specific risk factors, patients with known CADs are more vulnerable. Therefore, a good prediction tool should be used to guide preoperative evaluation and prioritization.

### Modification of the original RCRI

The RCRI is the most widely used risk stratification method. However, an unsatisfactory performance of the RCRI has been shown and its implementation in the modern surgical setting has been questioned<sup>10</sup> in vascular surgery and mixed noncardiac surgery.<sup>11–14</sup> In this study, the ability of the original RCRI to predict PoMCE in older patients with known CAD is relatively poor, with no better accuracy than that would be obtained by chance. In our study, the individual traditional components of the RCRI were not significantly associated with PoMCE, with the exception of insulin-dependent diabetes. The bad performance and low accuracy of the RCRI were not unanticipated. Advances in surgical, as well as anesthesia, practice combined with a more elaborate management regimen of CAD, make modern cardiac patients inherently different from the 1990s when the original RCRI

was developed and validated. The value of these original risk indicators in the RCRI may be diminishing over time. In earlier studies, the creatine kinase MB fraction was used to diagnose myocardial infarction, rather than troponins, which are more sensitive. Additionally, the original RCRI only considered in-patient complications, not 30-day event rates. A 30-day outcome, rather than in-hospital outcome parameters, should provide more clinical guidance.

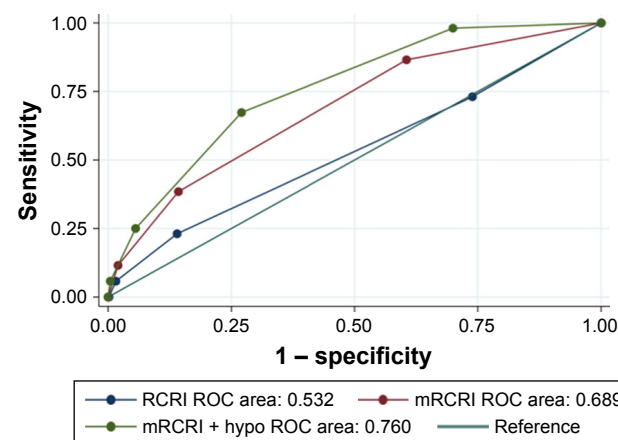
### Cerebrovascular disease

Conflicting results concerning the predictive power of cerebrovascular disease have been shown in other studies.<sup>15,16</sup> In our study, a history of cerebrovascular disease failed to predict PoMCE in older patients with CAD who underwent noncardiac surgery. Traditionally, the degree of stenosis and atherosclerotic plaque formation were believed to be similar between the coronary artery and cerebrovasculature. However, stroke is inherently different from myocardial infarction. The classical theory of myocardial infarction is rupture of existing atherosclerotic plaques due to instability and subsequent exposure of a prothrombotic surface, platelet adherence, and vessel thrombosis.<sup>17,18</sup> However, occurrence

**Table 4** Multivariate analysis of RCRI and modified RCRI

Variable	OR	CI	P-value
<b>RCRI</b>			
History of ischemic heart disease	NA		
History of congestive heart failure	0.97	0.09–6.07	0.984
Insulin-dependent diabetes mellitus	2.38	1.11–5.11	0.026
Creatinine >2 mg/dL	2.60	0.31–22.02	0.381
High-risk surgery	0.82	0.45–1.50	0.515
History of cerebrovascular disease	0.87	0.33–2.27	0.782
<b>mRCRI</b>			
History of myocardial infarction	3.23	1.61–6.51	0.01
Age >70 years	2.08	1.12–3.87	0.02
Insulin-dependent diabetes mellitus	3.03	1.41–6.49	0.00
Female	2.25	1.21–4.20	0.01
BMI <18 (kg/m <sup>2</sup> )	4.29	1.61–11.42	0.00
Optime >2.5 h	2.39	1.31–4.36	0.00
Atrial fibrillation	3.40	1.89–6.12	0.00

**Abbreviations:** BMI, body mass index; mRCRI, modified RCRI; NA, not applicable; OR, odds ratio; RCRI, revised cardiac risk index.



**Figure 1** Comparison of the predictive ability of the RCRI and mRCRI by ROC analysis.

**Note:** The ROC curves for the RCRI model (dotted blue line), the mRCRI model (dotted red line), and the model incorporating intraoperative hypotension (dotted green line) are shown.

**Abbreviations:** hypo, intraoperative hypotension; mRCRI, modified RCRI; RCRI, revised cardiac risk index; ROC, receiver operating characteristic.

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of stroke is more complicated and is affected by hemodynamic instability, comorbidity, such as atrial fibrillation, and intracranial vessel formation. A history of peripheral artery disease is suggested to be a good replacement factor for cerebrovascular disease in predicting cardiac risk in noncardiac surgery.<sup>19</sup> Peripheral disease is independently predictive of cardiac injury in the presence of cerebrovascular disease,<sup>20</sup> indicating the different nature of progression of disease.

## Creatinine

Use of cutoff values of 2 mg/dL of creatinine, regardless of age, sex, and BMI, has been questioned.<sup>21</sup> In our study, although overall creatinine levels were significantly different between patients with PoMCE and those without PoMCE, the cutoff value of 2 mg/dL failed to demonstrate predictive power. In fact, encountering patients with a creatinine level so high in modern clinical settings is rare. Use of the estimated glomerular filtration rate instead of creatinine has been suggested.<sup>22</sup> However, a study with strong clinical evidence on this issue has not been performed yet. Considering the poor performance of creatinine levels  $>2$  mg/dL, it has been removed from the original RCRI.

## Adding new elements to the mRCRI

A risk prediction model must have a good discriminatory ability, while remaining easy to use. Multiple modifications have been proposed, including age,<sup>10</sup> a history of peripheral vascular disease,<sup>20</sup> functional capacity,<sup>23</sup> preoperative N-terminal pro-brain natriuretic peptide levels,<sup>24</sup> and a specific surgical procedural category. In our study, the mRCRI incorporating age, female sex, atrial fibrillation, a history of myocardial infarction, and intraoperative hypotension showed better ability in predicting PoMCE in Chinese patients with CAD.

## Advanced age

Age is an independent predictor of cardiovascular events in the presence of RCRI risk factors and intraoperative risk factors.<sup>10</sup> Increased age might control for an increased risk associated with a longer duration of exposure to a clinical risk factor. However, in our study, an age  $>70$  years was strongly correlated with PoMCE after adjusting for the other components that are incorporated into the mRCRI. The lack of dynamic compensating ability of the cardiac vascular system among older people represents a unique cardiac risk. A large Danish national study reported an increased risk of MACE in patients with advanced age, with an OR of 1.9.<sup>25</sup> As the life expectancy of the general population in China

continues to grow, recognition of the risk of advanced age on cardiac events is important.

## Atrial fibrillation

Perioperative cardiac management is often complicated by cardiac arrhythmias, and the most common type of arrhythmia is atrial fibrillation.<sup>26</sup> Atrial fibrillation is common in older patients and patients with ischemic heart disease. The preoperative presence of atrial fibrillation may indicate previous myocardial infarction undetected by the patient. The China Acute Myocardial Infarction registry showed that the overall incidence of atrial fibrillation was 3.0% in Chinese patients with acute myocardial infarction during hospitalization.<sup>27</sup> This study demonstrated an even higher presence of atrial fibrillation in patients with PoMCE. The CHADS2-VASc is able to predict mortality in patients with atrial fibrillation undergoing noncardiac surgery.<sup>28</sup> Components of the CHADS2-VASc, including sex and age, have also been incorporated in the mRCRI. Without appropriate antithrombotic treatment, the risk of myocardial infarction due to coronary embolism is also increased. Incorporation of atrial fibrillation in this risk stratification model would help more patients to be prioritized.

## Female sex

A previous study attributed a sex difference in perioperative cardiac risk to the fact that women enrolled in the study were generally older and had more baseline cardiovascular risk factors.<sup>29</sup> In our study, female sex remained an independent predictor of PoMCE after adjustment for other risk factors in multivariate analysis. One retrospective registry of patients with ST segment elevation myocardial infarction showed that women have a longer time from symptom onset to hospital arrival and fewer complete revascularizations compared with men,<sup>30</sup> indicating a lack of self-recognition and unwillingness to obtain prompt treatment. Underreported and undertreated comorbidities could be a possible reason for a higher perioperative cardiac risk. Another possible explanation is that because women in our study population were older, they were more likely to have lost the cardiac protective effect from estrogen after menopause.

## Low body mass index

Overweight and obesity are risk factors for cardiovascular disease, including ischemic heart disease. However, a high BMI was not found to be a risk factor for perioperative cardiac morbidity in numerous previous studies.<sup>31</sup> Underweight

patients have a significantly increased risk of postoperative cardiac mortality and morbidity.<sup>32</sup> This phenomenon has been termed as the obesity paradox because of the seemingly protective effect of high BMI in terms of adverse cardiac events. In our study, a low BMI, perhaps a consequence of underlying nutritional status, was an independent risk factor of PoMCE. Although the underlying mechanism of this finding requires further research, recognizing a low BMI as a cardiac risk factor for cardiac patients is important.

### Intraoperative parameters

The effect of risk associated with surgery itself is crucial. In our study, univariate analysis showed that the risk of PoMCE among different surgery types was different. However, the original RCRI defines high-risk surgery as suprainguinal vascular, intraperitoneal, or intrathoracic surgery. This surgery component was not a predictor of PoMCE in this study. With advancement in the endoscopic minimally invasive technique, allocation of surgical risk is more complicated. Dangerous elements associated with surgery, including hemodynamic instability and severe physiological disturbance, cannot be defined by the operative site only. However, intraoperative parameters may be a more ideal replacement.

Cardiovascular risk prediction models rarely incorporate intraoperative physiological responses, such as hypotension, tachycardia, or hypothermia. Because preoperative risk factors are unlikely to predict intraoperative parameters, inclusion of intraoperative risk factors should be considered. Tachycardia and hypotension are thought to be associated with postoperative cardiac complications. In our cohort study, intraoperative hypotension was an independent risk factor for PoMCE. With the added predictive value of intraoperative hypotension, the predictive ability significantly improved. Additionally, a longer surgical time was associated with postoperative cardiac events. To the best of our knowledge, this is the first study to incorporate intraoperative parameters into a risk prediction model.

### Conclusion

Patients with known CAD have unique challenges in terms of cardiac risk assessment and management. Identification of increased risk provides patients with information that helps them better understand the benefit-to-risk ratio of a procedure and may lead to interventions that decrease the risk. Some traditional risk prediction parameters in the RCRI are no longer suitable in the modern clinical setting and have poor prediction ability in older Chinese patients

with CAD. A modified model incorporating advanced age, sex, atrial fibrillation, insulin-dependent diabetes, a history of myocardial infarction, and intraoperative parameters can possibly provide better predictive power. Additionally, this model could guide perioperative management of cardiac patients undergoing noncardiac surgery.

### Limitations of this study

Because this was a post-hoc analysis, some important data related to PoMCE, such as (N-terminal pronatriuretic peptide) NT-pro brain natriuretic peptide and glomerular filtration rate, were not available in the database. The primary end point was 30-day postoperative cardiac events, and long-term prognoses of these patients were unknown. Although this was a multicenter study, the sample size of this study was still insufficient because the incidence of certain clinical events was too low to generate any statistically powerful results. Medication history was not included in this study due to no protective power against adverse cardiac events in previous study using the same database. However, in other trials, medication was demonstrated to potentially influence prognosis. This problem may be better evaluated in future clinical trials with larger sample size.

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### Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

### Disclosure

The authors report no conflicts of interest in this work.

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