의학박사 학위논문

# Comparative Analysis of Perioperative Myocardial Infarction Criteria in Predicting Outcomes After Coronary Artery Bypass Surgery

## 관상동맥우회술 이후 결과 예측에 있어 주술기 심근경색 진단기준의 비교 분석

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이 논문을 의학박사 학위 논문으로 제출함

2024년 8월

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## Abstract

### Background

There have been various definitions for perioperative myocardial infarction (pMI) following coronary artery bypass grafting, but it is unclear which definition is most relevant. The purpose of this study is to (i) investigate the association between the various pMI definitions and postoperative mortality and (ii) identify the definition that has the greatest incremental value in predicting postoperative mortality.

### Methods

The study examined a cohort of 3,211 patients undergoing elective coronary artery bypass grafting at a tertiary hospital in Korea. The prognostic value of perioperative myocardial infarction was assessed according to six different pMI definitions: (i) the 4th Universal Definition of Myocardial Infarction (4UD), (ii) the Academic Research Consortium (ARC), (iii) the Society for Cardiovascular Angiography and Interventions (SCAI), (iv) the Valve Academic Research Consortium (VARC), (v) the European Association of Cardio-Thoracic Surgery (EACTS), and (vi) the myocardial injury criteria proposed by the Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study. The co-primary endpoints of the study were operative mortality (all-cause mortality within 30 days of surgery or before discharge) and postoperative 1-year all-cause mortality. The incremental prognostic value of each definition was evaluated using the area under the receiver operating characteristic curve (AUC), likelihood ratio tests, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

### Results

The operative mortality rate was 1.3% (42 of 3,211), and the 1-year mortality rate was 3.4% (109 of 3,211). The VISION myocardial injury criteria showed the strongest independent association with operative mortality [odds ratio (OR) 5.27; 95% confidence interval (CI) 2.84 to 9.79; 4UD: OR 3.49; 95% CI 1.47 to 5.74; ARC: OR 3.49; 95% CI 1.70 to 7.20; SCAI: OR 2.54; 95% CI 1.38 to 4.67; VARC: OR 2.43; 95% CI 1.32 to 4.49; EACTS: OR 3.29; 95% CI 1.75 to 6.19]. The VISION criteria

had the highest incremental value in predicting operative mortality (AUC 0.78; Chi-square statistic 24.19; NRI 0.325; IDI 0.0116). On the other hand, 4UD showed the strongest association with 1-year mortality [hazard ratio (HR) 3.29; 95% confidence interval (CI) 2.18 to 4.97; ARC: HR 2.92; 95% CI 1.83 to 4.67; SCAI: HR 2.16; 95% CI 1.48 to 3.15; VARC: HR 2.32; 95% CI 1.60 to 3.38; EACTS: HR 3.09; 95% CI 2.08 to 4.58; VISION: HR 2.25; 95% CI 1.47 to 3.44]. The 4UD and EACTS criteria demonstrated the most significant incremental value for predicting 1-year mortality (4UD: AUC 0.77, Chi-square statistic 26.91, NRI 0.324, IDI 0.0063; EACTS: AUC 0.76, Chi-square statistic 27.37, NRI 0.349, IDI 0.0055).

**Conclusions**

Among various definitions for pMI following coronary artery bypass grafting, the VISION myocardial injury criteria provide the greatest incremental value in predicting operative mortality, whereas the 4UD and EACTS definitions of Myocardial Infarction are the most effective predictors of 1-year all-cause mortality.

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## Introduction

Coronary artery bypass grafting (CABG) is the preferred treatment for advanced coronary artery disease, particularly left main disease and multivessel disease with ischemic cardiomyopathy.[1] While CABG is well known for its life-extending benefits, there is a risk of perioperative myocardial injury, which may occur as a consequence of surgical damage, ischemia-reperfusion injury, or other perioperative insults.[2-4] Such myocardial injury may cause perioperative myocardial infarction (pMI), which is classified as Type 5 myocardial infarction, a complication associated with a higher mortality risk.[3,5] Therefore, establishing reliable diagnostic criteria for pMI is crucial to enhancing patient care. Despite this, various organizations have proposed different definitions of pMI following coronary artery bypass surgery. There are several major definitions, including the 4th Universal Definition of Myocardial Infarction (4UD),[5] those proposed by the Academic Research Consortium (ARC)-2,[6] the Society for Cardiovascular Angiography and Interventions (SCAI),[7] the Valve Academic Research Consortium (VARC) 3,[8] and the European Association of Cardio-Thoracic Surgery (EACTS).[4] There are significant differences in the criteria among these definitions, including the types of biomarkers and cut-off levels, as well as clinical criteria such as new electrocardiogram (ECG) abnormalities, evidence of myocardial ischemia, angiographic evidence of graft or native vessel occlusion, and the presence of criteria based solely on biomarkers. Additionally, the recent Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study advocates significantly higher cut-off levels of biomarker than previous diagnostic criteria.[9]

This variety of standards has resulted in significant discrepancies in the reported incidence of pMI and its associated prognostic implications. Therefore, there is considerable uncertainty regarding the diagnostic criteria to be applied in clinical settings to diagnose pMI. Furthermore, there is no consensus about which criteria should be used for outcomes in clinical trials and, most importantly, which are most accurate for predicting patient outcomes. As a result, research is needed to determine the optimal diagnostic criteria for pMI and its true prognostic significance.

In this clinical context, this observational study was designed to provide insight into the optimal definition of pMI. Our specific objectives are to determine whether a variety of pMI definitions are associated with postoperative short-term and long-term mortality, and to determine which definition is the most useful in predicting mortality.

## Methods

### *Study design and participants*

This observational study included patients who underwent elective CABG at a tertiary academic center in Seoul, South Korea from January 2006 to December 2019. Participants without preoperative cardiac biomarker data for pMI assessment were excluded. Asan Medical Center's Institutional Review Board has approved this observational study (protocol number 2024-0142), and informed consent was waived due to the retrospective nature of the study. Data were derived from the Asan Medical Center Cardiovascular Surgery and Anesthesia Database in conjunction with electronic medical records.

### *Definition of the pMI criteria*

The exposure of interest for this study consists of five pMI criteria and one myocardial injury criteria. These criteria include those adopted from the 4th Universal Definition of Myocardial Infarction (4UD), Academic Research Consortium (ARC), Society for Cardiovascular Angiography and Interventions (SCAI), Valve Academic Research Consortium (VARC), European Association of Cardio-Thoracic Surgery (EACTS), and the Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study. In all definitions, troponin is the most commonly used biomarker, while SCAI and VARC also consider creatine kinase-MB (CK-MB) as the primary biomarker. In terms of troponin cut-off values, there is a noticeable difference among these criteria. 4UD and EACTS adopted a relatively low threshold of >10 times the upper normal limit (UNL), while ARC, SCAI, and VARC recommended a higher cut-off level of 35 times the UNL. VISION advocates the highest troponin thresholds, with > 218×UNL on day 1 and > 59×UNL on days 2 and 3. Clinical criteria are included in most definitions, except for VISION, which does not include any clinical criteria. There are several clinical criteria, including new Q waves, new regional wall abnormalities, and new graft or coronary occlusions. Additionally, SCAI, VARC, and EACTS provide additional criteria based exclusively on biomarker elevations. Table 1 summarizes each diagnostic criteria.

**Table 1. Summary of Diagnostic Criteria for Perioperative Myocardial Infarction and Myocardial Injury**

| | 4UD | ARC | SCAI | VARC | EACTS | VISION myocardial injury |
|---|---|---|---|---|---|---|
| Cardiac biomarker | Troponin | Troponin | CK-MB Troponin in the absence of CK-MB | CK-MB Troponin in the absence of CK-MB | Troponin | Troponin |
| Cut-off value | >10×UNL | ≥ 35×UNL | ≥ 5×UNL for CK-MB ≥ 35×UNL for troponin | ≥ 5×UNL for CK-MB ≥ 35×UNL for troponin | >10×UNL | > 218×UNL (<=1day), >59×UNL (2,3 day) |
| Cut-off for elevated baseline | >20% rise & >10×UNL | - | Increased CK-MB ≥ 5×UNL Increased troponin ≥ 35×UNL | Increased CK-MB ≥ 5×UNL Increased troponin ≥ 35×UNL | - | - |
| Clinical criteria | 1 of the fallowing | 1 of the fallowing | ECG only | 1 of the fallowing | 1 of the fallowing | NA |
| New Q waves | + | + | + | + | + | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| New LBBB | - | - | + | + | - | NA |
| New graft/coronary occlusion | + | + | - | + | + | NA |
| New RMWA | + | + | - | + | + | NA |
| Biomarker only pathway | - | - | + | + | + | NA |
| Cut-off value | NA | NA | ≥ 10×UNL for CK-MB ≥ 70×UNL for troponin | ≥ 10×UNL for CK-MB ≥ 70×UNL for troponin | > 500× UNL | NA |
| Vs. periprocedural MI criteria for PCI | Twice the cut-off value | Same | Same | Same | NA | NA |

4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation, UNL: Upper Normal Limit, ECG: Electrocardiogram, RMWA: Regional Wall Motion Abnormality, CK-MB: Creatine Kinase-MB, LBBB: Left Bundle Branch Block, MI: myocardial infarction, PCI: Percutaneous Coronary Intervention.

We routinely measured cardiac biomarkers preoperatively, immediately after surgery, on the evening of surgery day, and on postoperative days 1 and 2, with additional measurements when necessary. The biomarkers were measured using Centaur XPT or Atellica IM systems (Siemens, Erlangen, Germany). Clinical criteria were determined based on perioperative serial ECGs, transthoracic echocardiograms, and coronary angiography, which were performed when necessary.

***Outcomes and covariables***

We explored coprimary outcomes in this study to assess the short- and long-term consequences of pMI. For short-term outcomes, we used operative mortality, which was defined as death occurring within 30 days of surgery or before discharge from the hospital.[10] The long-term outcome was postoperative 1-year all-cause mortality. The patients' survival status was determined by Korea's national health insurance status.

We used the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), a widely accepted model for risk stratification in cardiovascular surgery, as the primary covariable in our analysis.[11] EuroSCORE II incorporates a number of patient, cardiac, and surgical characteristics, such as age, sex, comorbidities, ejection fraction, the New York Heart Association classification, recent MI, pulmonary hypertension, and resting angina. Currently, the model is widely used and well-validated to assess the risks associated with CABG.

***Statistical analysis***

To maximize statistical power, all available patients were included in our study without performing a predetermined sample size calculation. Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR), while categorical variables were reported as numbers and proportions. The baseline characteristics of the groups were compared using Fisher's exact test, chi-square test, Student's t-test, or Wilcoxon rank-sum test as appropriate.

To investigate operative mortality, logistic regression was used, and to investigate postoperative 1-year all-cause mortality, Cox-proportional hazards regression was utilized. At first, we employed a null model containing only EuroSCORE II as a variable. We then developed a model that included EuroSCORE II and each pMI criteria. The risks associated with each pMI definition were quantified as adjusted odds ratios and 95% confidence intervals (CI) for operative mortality and adjusted hazard ratios with 95% CI for 1-year all-cause mortality. The survival data was visualized using Kaplan-Meier curves, and the proportionality assumption was checked using log-log plots.

To assess the incremental value of each pMI criteria, several statistical methods were applied. First, by using Receiver Operating Characteristic (ROC) curves, the models' discriminative ability was evaluated by their Area Under the Curve (AUC). Second, the likelihood ratio test was used to determine whether the addition of additional predictors (i.e., pMI criteria) significantly improved the overall fit of nested models. A chi-square statistic derived from the likelihood ratio test quantifies the incremental value of the new model over the null model. Third, Net Reclassification Improvement (NRI) was utilized to quantify how the new model enhances prediction at the patient level. NRI quantifies the proportion of individuals correctly reclassified into higher or lower risk categories by the new model. Fourth, Integrated Discrimination Improvement (IDI) was applied to measure the absolute improvement in the prediction accuracy of the new model. The IDI measures the increase in discrimination gradient, which represents the difference in average predicted probabilities between the null model and the new model.

To ensure the robustness of our findings, we conducted two sensitivity analyses. In the first analysis, only data from the most recent ten years were included. As part of the second analysis, additional surgical factors such as off-pump CABG (OPCAB) and surgical duration were added to EuroSCORE II, allowing for the consideration of surgical insult, one of the key mechanisms in pMI development.

P-values reported in analyses that assess the incremental value of each pMI criteria are based on comparisons with a null model. Since this study was exploratory, the p-values were not adjusted for multiple comparisons; therefore, a two-sided P-value of less than 0.05 was considered statistically

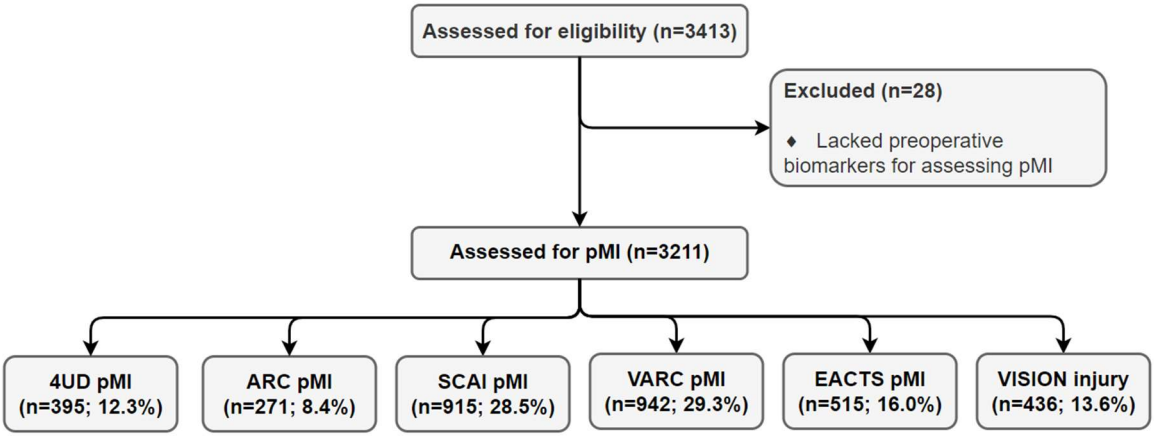
significant. R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

## Results

### *Study population and baseline characteristics*

During the study period, 3,413 patients were assessed for eligibility. Of these, 28 patients were excluded due to the absence of preoperative biomarkers to assess pMI. A total of 3,211 patients were considered eligible for further analysis under various pMI definitions (Figure 1).

**Figure 1. Study Flow Diagram and pMI Incidence According to Different Criteria**




pMI: Perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

Depending on the diagnostic criteria used, there were substantial differences in the incidence of pMI. The pMI criteria proposed by the ARC resulted in the lowest incidence rate of 8.4%. This was followed by the 4UD, which identified 395 patients (12.3%) with pMI. Those criteria that included additional criteria based solely on biomarker elevations, such as EACTS, SCAI, and VARC, demonstrated higher incidence in 515 (16.0%), 915 (28.5%), and 942 (29.3%) patients, respectively. In addition, 436 patients (13.6%) met the VISION myocardial injury criteria, which do not require clinical criteria.

Table 2 presents the study patients' baseline characteristics. The median age was 65 years and 24% were female. There were several significant differences between patients diagnosed with pMI and those without pMI across a variety of diagnostic criteria. Patients with pMI had a higher proportion of New York Heart Association classification III or IV. Patients with pMI also had lower left ventricular ejection fractions and higher EuroSCORE. As for surgical characteristics, pMI patients were less likely to undergo OPCAB and had longer surgical durations.

**Table 2. Patient characteristics according to different pMI criteria**

| | All patients (N = 3211) | 4UD (N = 395) | ARC (N = 271) | SCAI (N = 915) | VARC (N = 942) | EACTS (N = 515) | VISION (N = 436) |
|---|---|---|---|---|---|---|---|
| Age (years) | 65 [58 to 71] | 65 [59 to 71] | 65 [60 to 70] | 65 [59 to 71] | 65 [59 to 71] | 65 [59 to 71] | 65 [59 to 71] |
| Female sex | 771 (24.0%) | 76 (19.2%)* | 59 (21.8%) | 225 (24.6%) | 232 (24.6%) | 105 (20.4%) | 105 (24.1%) |
| BMI ($kg.m^{-2}$) | 24.5 [22.7 to 26.4] | 24.4 [22.6 to 26.1] | 24.4 [22.6 to 26.2] | 24.6 [22.8 to 26.5] | 24.6 [22.8 to 26.5] | 24.4 [22.6 to 26.2] | 24.6 [22.8 to 26.4] |
| DM | 1627 (50.7%) | 201 (50.9%) | 132 (48.7%) | 431 (47.1%)* | 445 (47.2%)* | 257 (49.9%) | 219 (50.2%) |
| Hypertension | 2068 (64.4%) | 244 (61.8%) | 161 (59.4%) | 594 (64.9%) | 610 (64.8%) | 327 (63.5%) | 289 (66.3%) |
| Dyslipidemia | 2082 (64.8%) | 239 (60.5%) | 152 (56.1%) | 583 (63.7%) | 600 (63.7%) | 313 (60.8%)* | 243 (55.7%)* |
| Previous coronary revascularization | 637 (19.8%) | 77 (19.5%) | 51 (18.8%) | 189 (20.7%) | 198 (21.0%) | 107 (20.8%) | 104 (23.9%)* |
| Cerebrovascular disease | 632 (19.7%) | 81 (20.5%) | 61 (22.5%) | 209 (22.8%)* | 211 (22.4%) | 105 (20.4%) | 103 (23.6%)* |
| Peripheral vascular disease | 145 (4.5%) | 18 (4.6%) | 11 (4.1%) | 36 (3.9%) | 38 (4.0%) | 25 (4.9%) | 23 (5.3%) |
| COPD | 119 (3.7%) | 20 (5.1%) | 15 (5.5%) | 41 (4.5%) | 42 (4.5%) | 23 (4.5%) | 22 (5.0%) |
| Chronic kidney disease | 543 (16.9%) | 66 (16.7%) | 41 (15.1%) | 176 (19.2%)* | 179 (19.0%)* | 98 (19.0%) | 99 (22.7%)* |
| NYHA class III or IV* | 264 (9.5%) | 55 (15.7%)* | 40 (16.6%)* | 96 (11.9%)* | 97 (11.7%)* | 79 (17.1%)* | 64 (16.9%)* |
| Left ventricular ejection fraction (%) | 59 [49 to 64] | 55 [42 to 61]* | 55 [42 to 61]* | 58 [47 to 63] | 58 [47 to 63]* | 55 [41 to 61]* | 56.5 [44 to 62]* |
| EuroSCORE II | 1.2 [0.8 to 2.0] | 1.4 [0.9 to 2.5]* | 1.5 [0.9 to 2.5]* | 1.3 [0.8 to 2.3]* | 1.3 [0.8 to 2.2]* | 1.5 [0.9 to 2.6]* | 1.5 [0.9 to 2.7]* |
| Off-pump surgery | 2397 (74.6%) | 260 (65.8%)* | 158 (58.3%)* | 550 (60.1%)* | 372 (39.5%)* | 329 (63.9%)* | 179 (41.1%)* |
| Operation duration (min) | 230 [195 to 275] | 240 [205 to 295]* | 250 [213 to 305]* | 245 [205 to 300]* | 245 [205 to 300]* | 245 [205 to 303]* | 270 [220 to 335]* |
| Operative mortality (%) | 42 (1.3%) | 12 (3.0%)* | 10 (3.7%)* | 21 (2.3%)* | 21 (2.2%)* | 16 (3.1%)* | 19 (4.4%)* |
| 1-year mortality (%) | 109 (3.4%) | 33 (8.4%)* | 22 (8.1%)* | 50 (5.5%)* | 53 (5.6%)* | 39 (7.6%)* | 29 (6.7%)* |

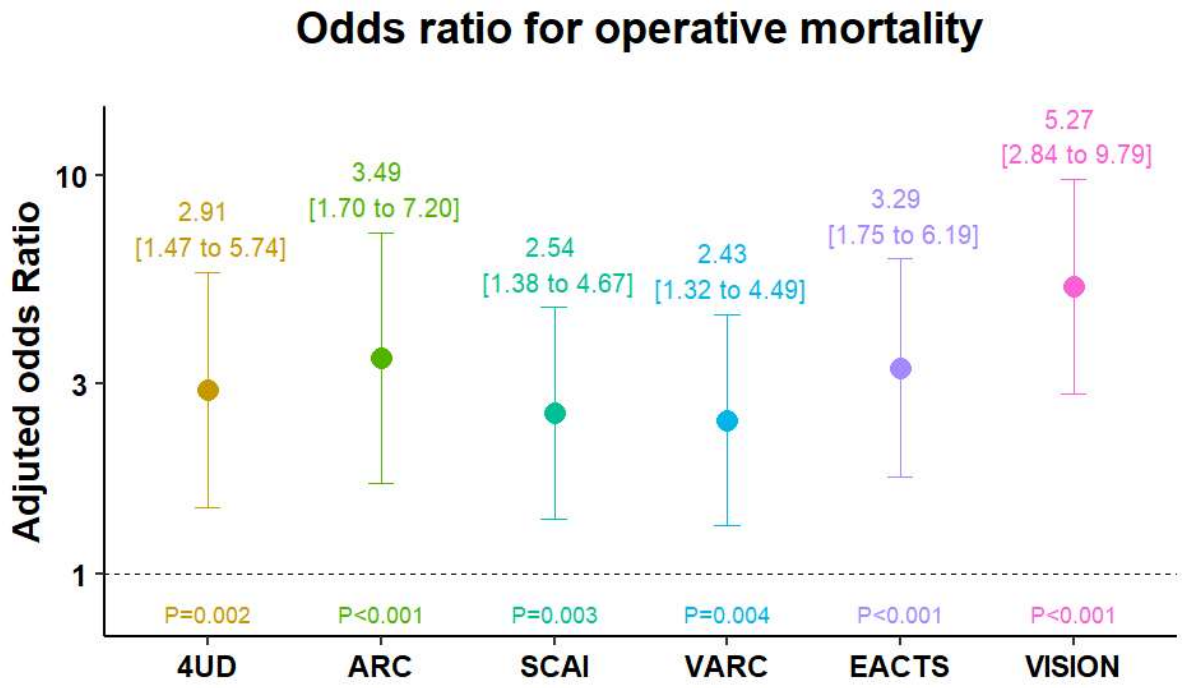
* Indicates a p-value < 0.05 when compared with patients without pMI.

pMI: perioperative myocardial infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort EvaluationBMI: Body Mass Index, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, NYHA: New York Heart Association, EuroSCORE: European System for Cardiac Operative Risk Evaluation.

***Operative mortality according to pMI criteria***

Among the 3,211 patients analyzed, 42 (1.3%) died within 30 days of surgery or before discharge. Figure 2 presents the odds ratios for operative mortality, adjusted for EuroSCORE II. All pMI criteria were independently associated with operative mortality. Among these criteria, the VISION myocardial injury criteria had the highest odds ratio of 5.27 [95% CI: 2.84 to 9.79].

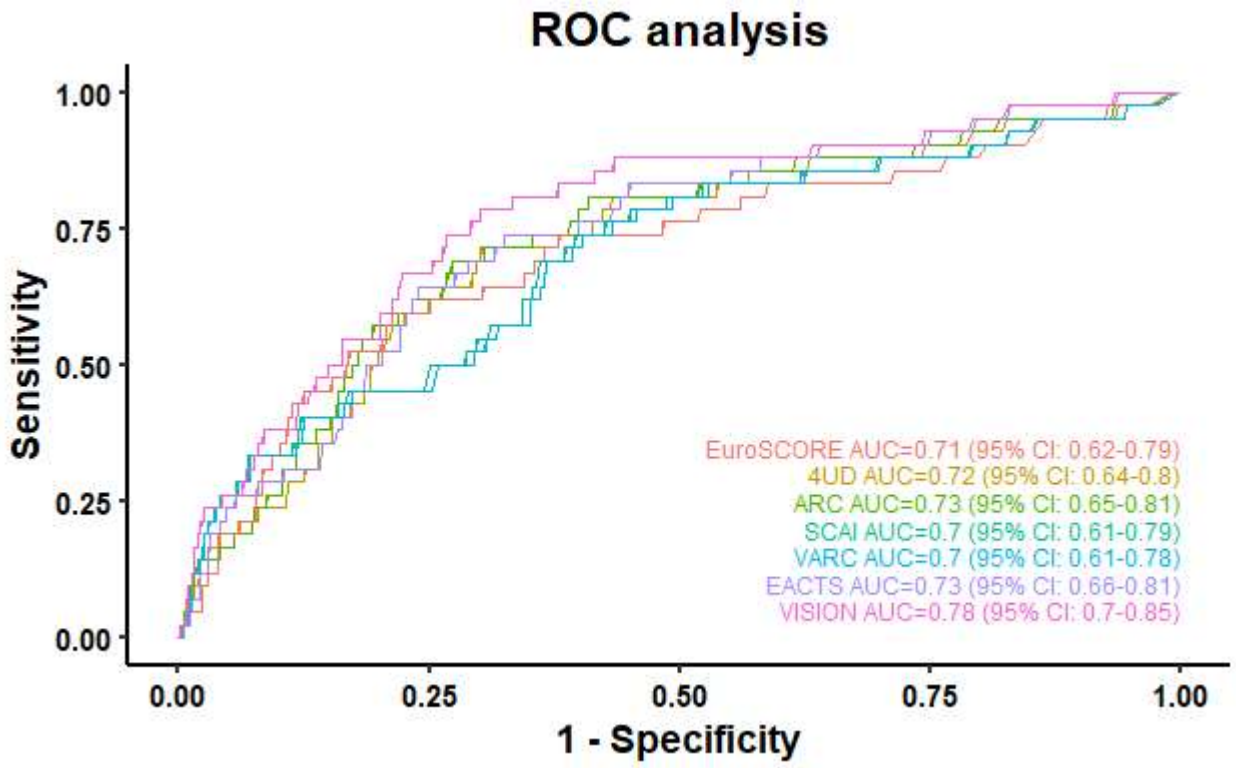
**Figure 2. Odds Ratios for Operative Mortality Adjusted for EuroSCORE II**




The dots represent the odds ratios, and the error bars indicate the 95% confidence intervals.
4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

Figure 3 shows the ROC curves for each model based on different pMI criteria. These pMI criteria demonstrated varying degrees of discriminative ability when added to the EuroSCORE, with AUC values ranging from 0.70 to 0.78. Although the differences were not statistically significant, the VISION criteria showed the highest AUC of 0.78.

**Figure 3. ROC Analysis for Operative Mortality**

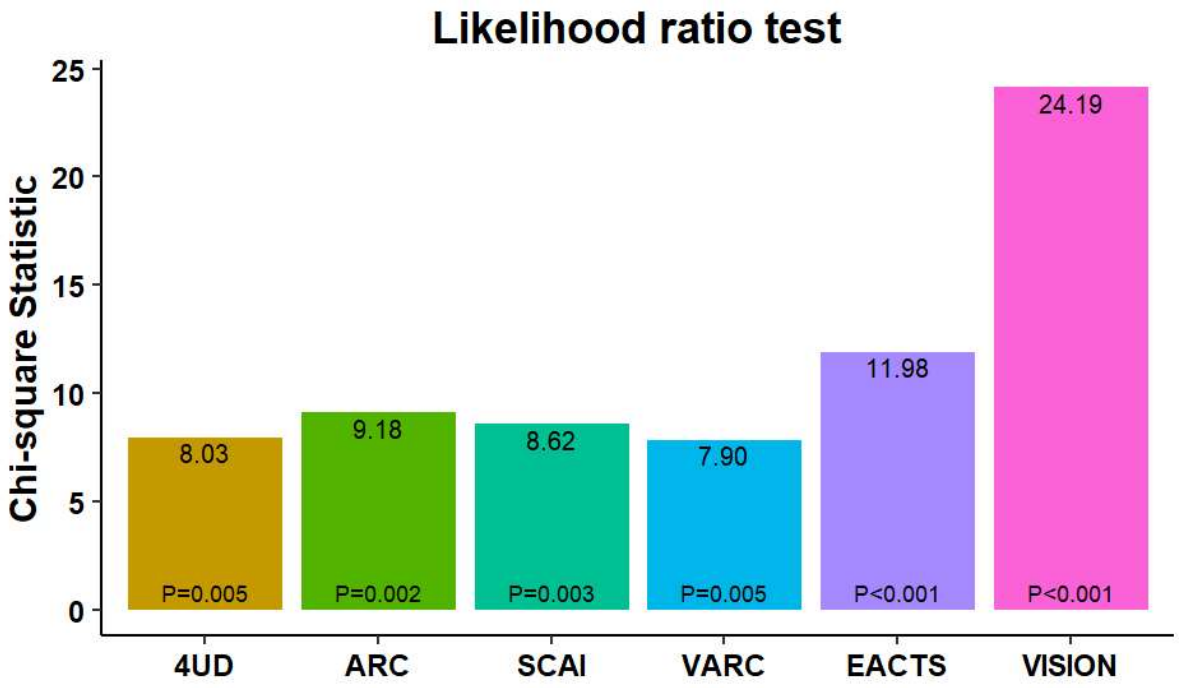



The ROC curves illustrate the discriminative ability of various pMI criteria for predicting operative mortality, with AUC values and their 95% CI as shown.

ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval, pMI: perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

In likelihood ratio tests, VISION criteria demonstrated the most significant improvement in model fit, as indicated by a chi-square statistic of 24.19 (Figure 4).

**Figure 4. Likelihood Ratio Test for Incremental Value of pMI Criteria**

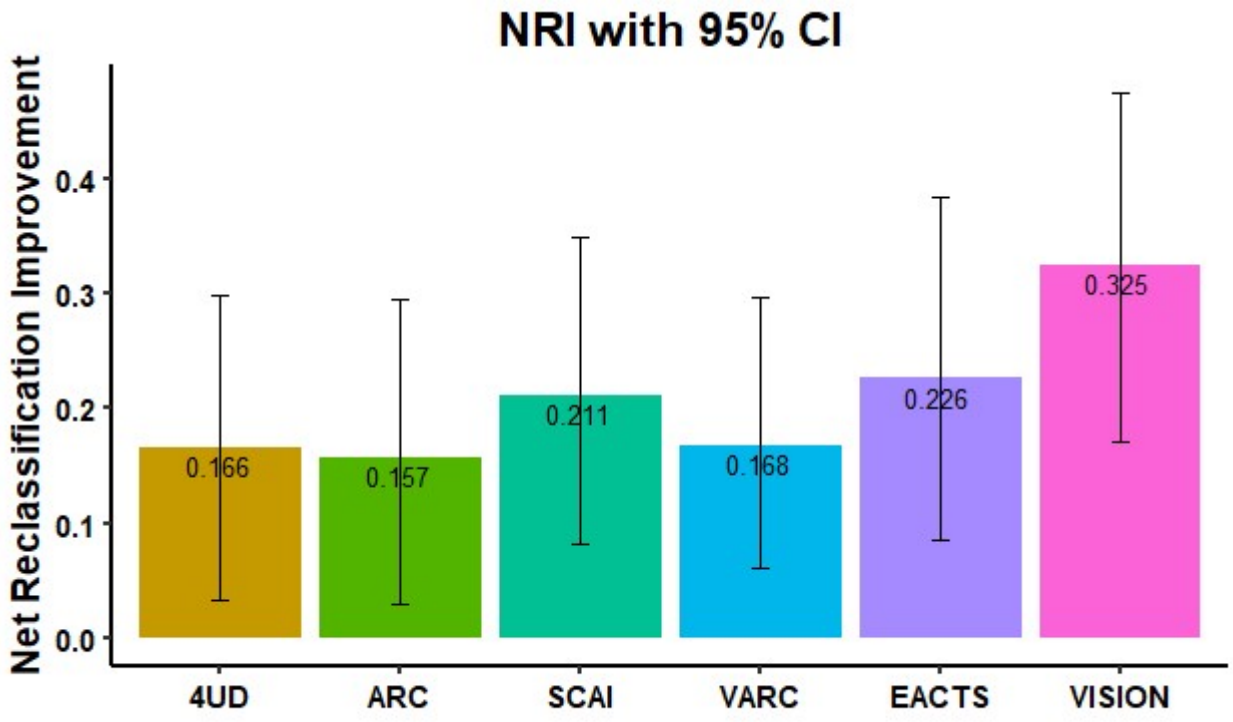



The likelihood ratio test results show the chi-square statistics for each pMI criterion, indicating the incremental value added to the baseline model for predicting operative mortality.

pMI: perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

Based on the NRI and IDI analyses, the VISION criteria demonstrated the most substantial improvements in the prediction of operative mortality, with an NRI of 0.325 and an IDI of 0.0116 (Figures 5 and 6).

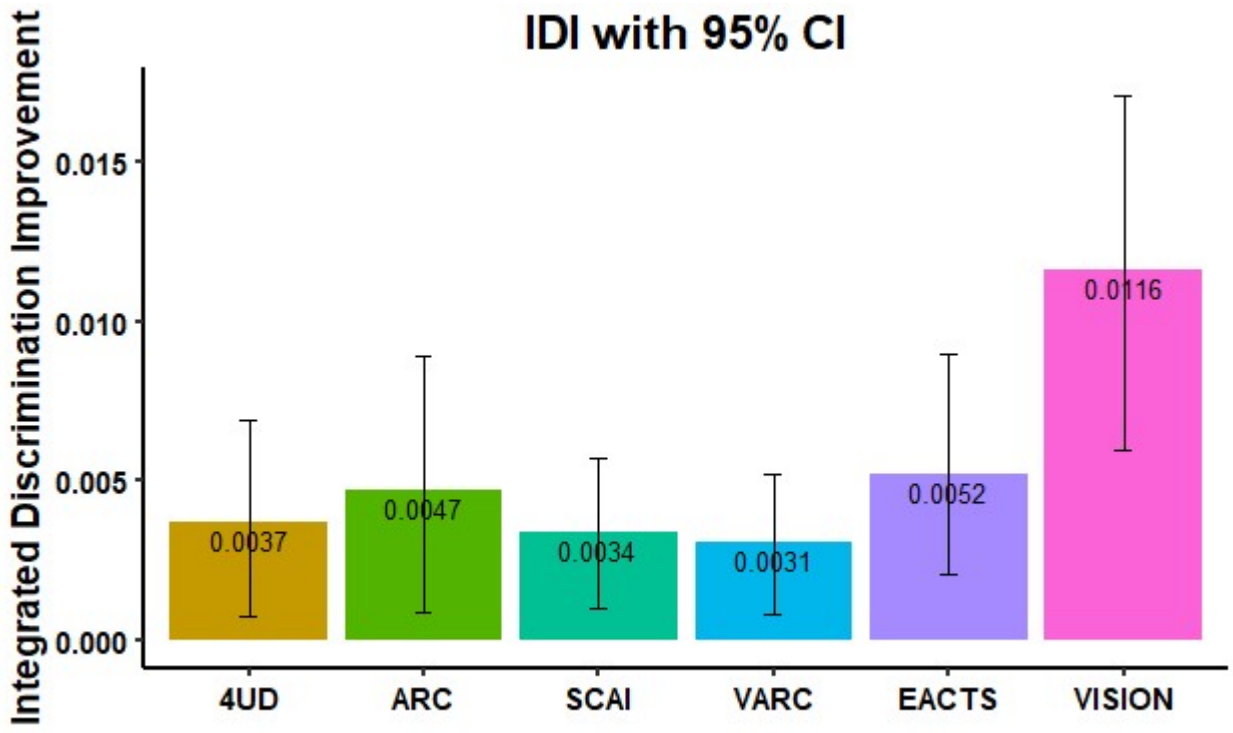
**Figure 5. Net Reclassification Improvement with 95% Confidence Intervals**




NRI values for each pMI criteria are presented with their 95% CI.

NRI: Net Reclassification Improvement, CI: confidence interval, pMI: Perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

**Figure 6. Integrated Discrimination Improvement with 95% Confidence Intervals**



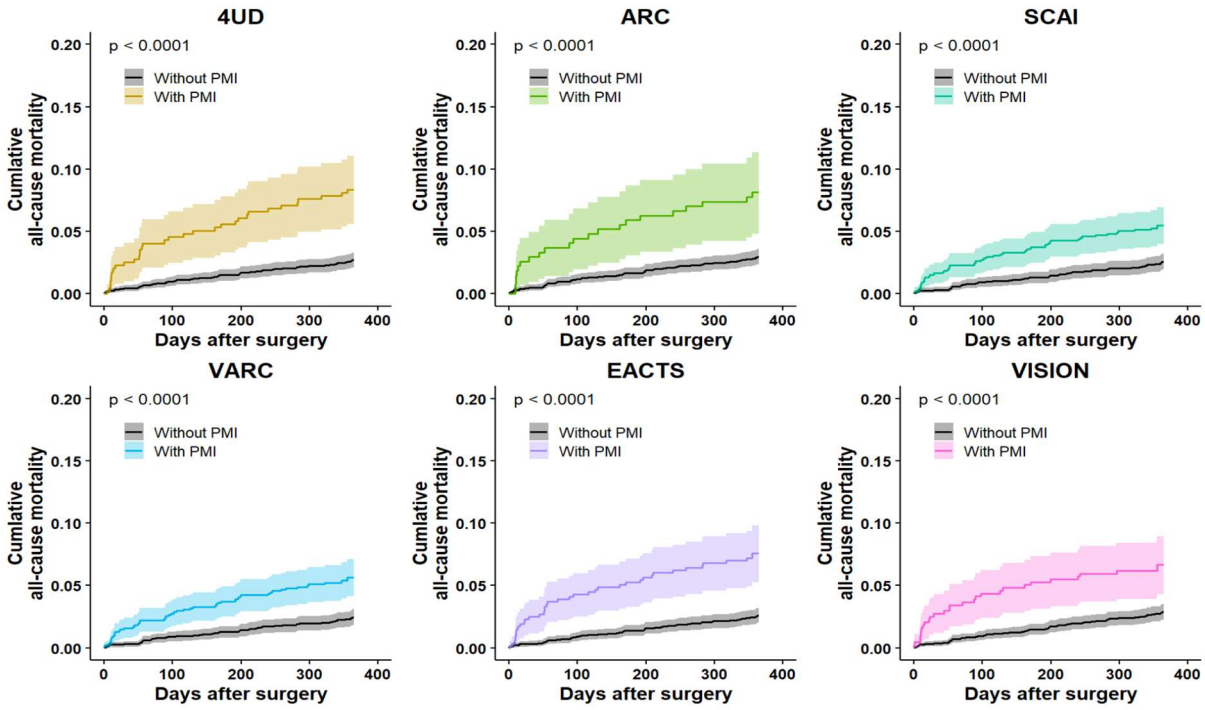

The IDI values for each pMI criteria are presented with their 95% CI.

IDI: Integrated Discrimination Improvement, CI: Confidence Interval, pMI: Perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

***Postoperative 1-year all-cause mortality according to pMI criteria***

Of the 3,211 patients, 109 (3.4%) died within postoperative 1-year. Across all pMI criteria, the Kaplan-Meier curves demonstrate a significant difference in cumulative mortality between patients with and without pMI (Figure 7).

**Figure 7. Cumulative all-cause mortality according to pMI criteria**

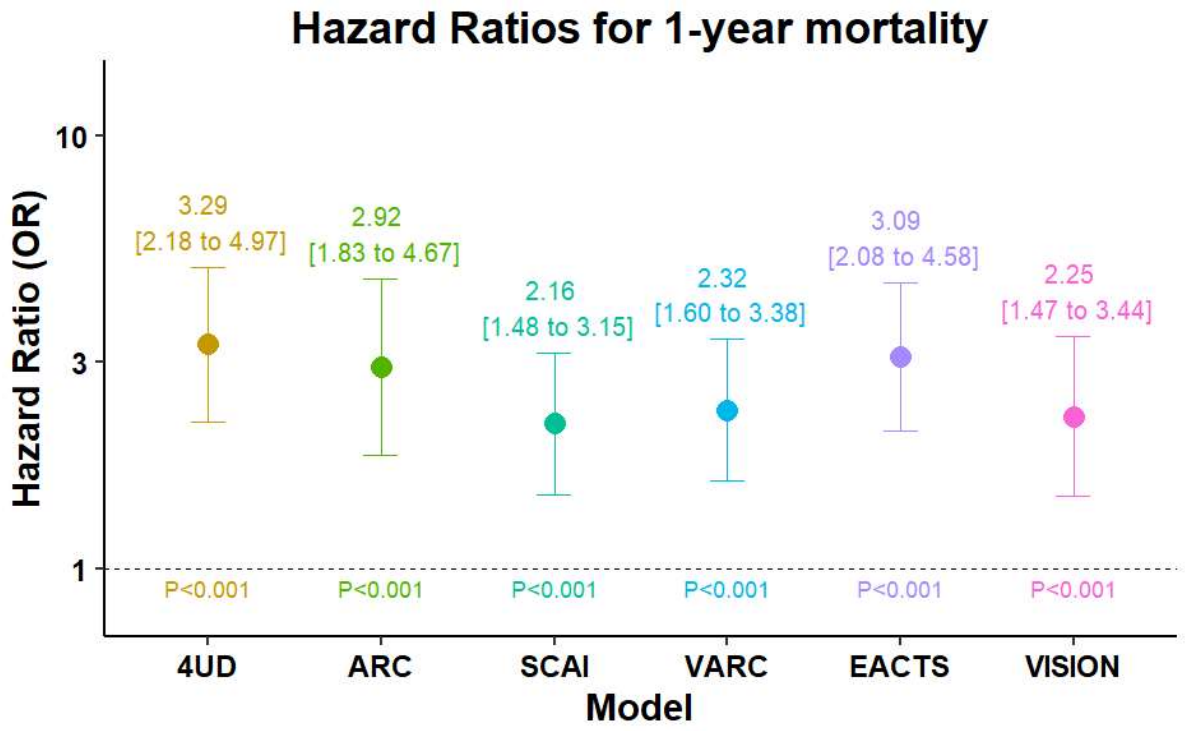



Cumulative all-cause mortality within postoperative 1 year stratified by the presence of pMI, as defined by six different criteria. Each graph compares patients with pMI (colored line) and without pMI (gray line) across different definitions. Shaded areas represent 95% confidence intervals. The p-values represent the results of log-rank test.

pMI: Perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

In terms of the hazard ratio for one-year mortality adjusted for EuroSCORE II, 4UD had the highest hazard ratio of 3.29 [95% CI 2.18-4.97]. It was followed by EACTS with a hazard ratio of 3.09 [95% CI 2.08-4.58] (Figure 8).

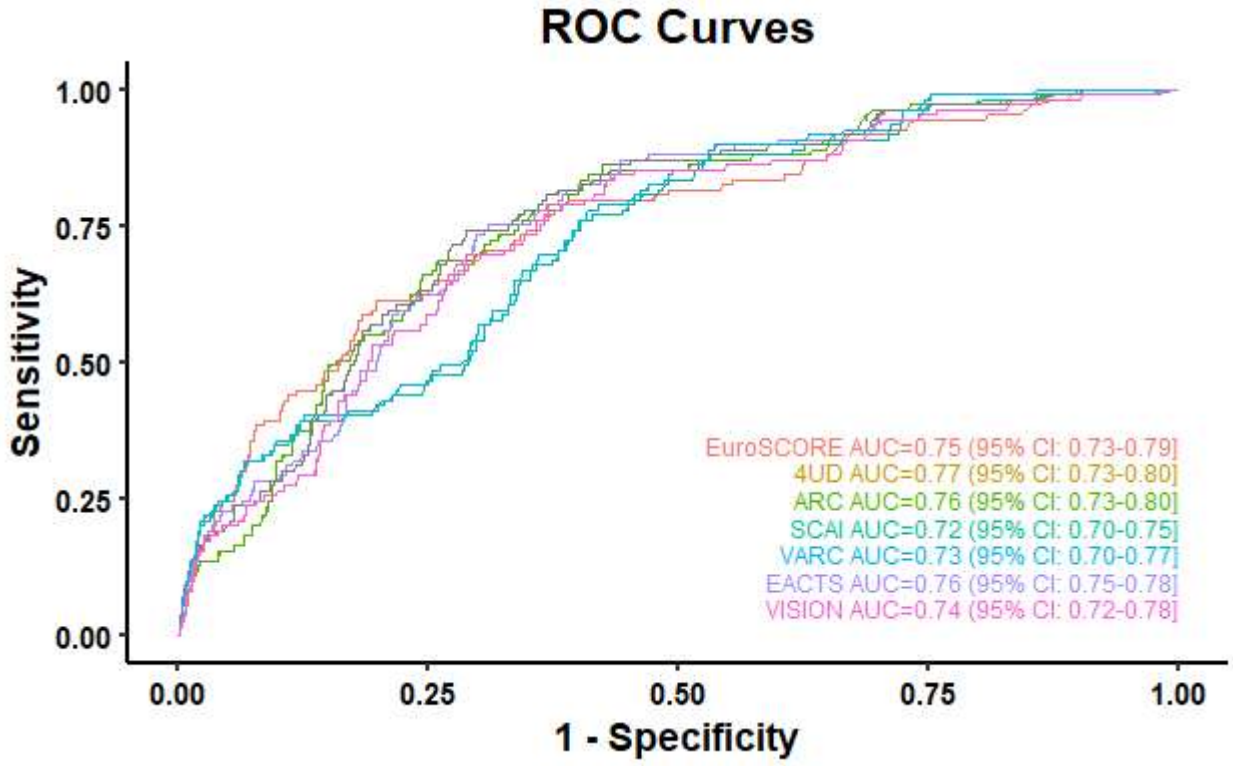
**Figure 8. Hazard Ratios for 1-year Mortality Adjusted for EuroSCORE II**




The dots represent the odds ratios, and the error bars indicate the 95% confidence intervals.
4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

As shown in Figure 9, ROC curve analysis for 1-year mortality revealed that the 4UD criteria, with an AUC of 0.77, had the highest discriminative ability, although it was only marginally better than EuroSCORE alone (AUC 0.75) and EACTS (AUC 0.76).

**Figure 9. ROC Analysis for 1-year Mortality**

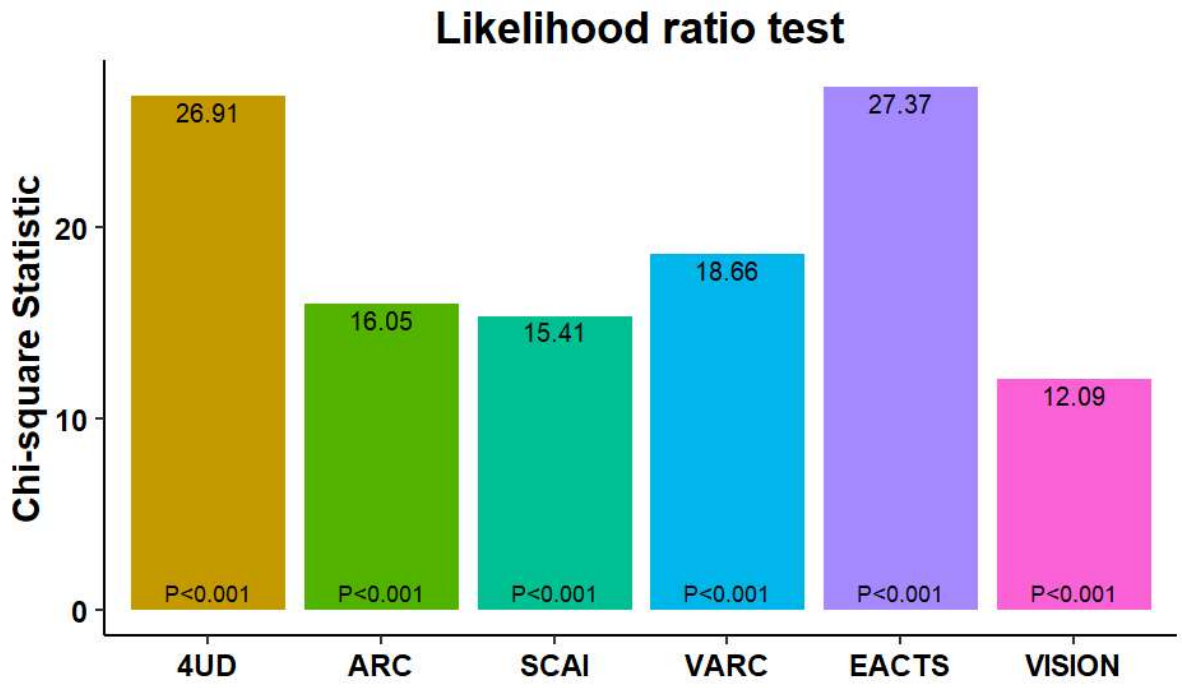



The ROC curves illustrate the discriminative ability of various pMI criteria for predicting 1-year mortality, with AUC values and their 95% CI as shown.

ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval, pMI: perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

In the likelihood ratio test, the EACTS criteria had the highest chi-square statistic of 27.37, which was closely followed by the 4UD criteria with a chi-square of 26.91 (Figure 10).

**Figure 10. Likelihood Ratio Test for Incremental Value of pMI Criteria**

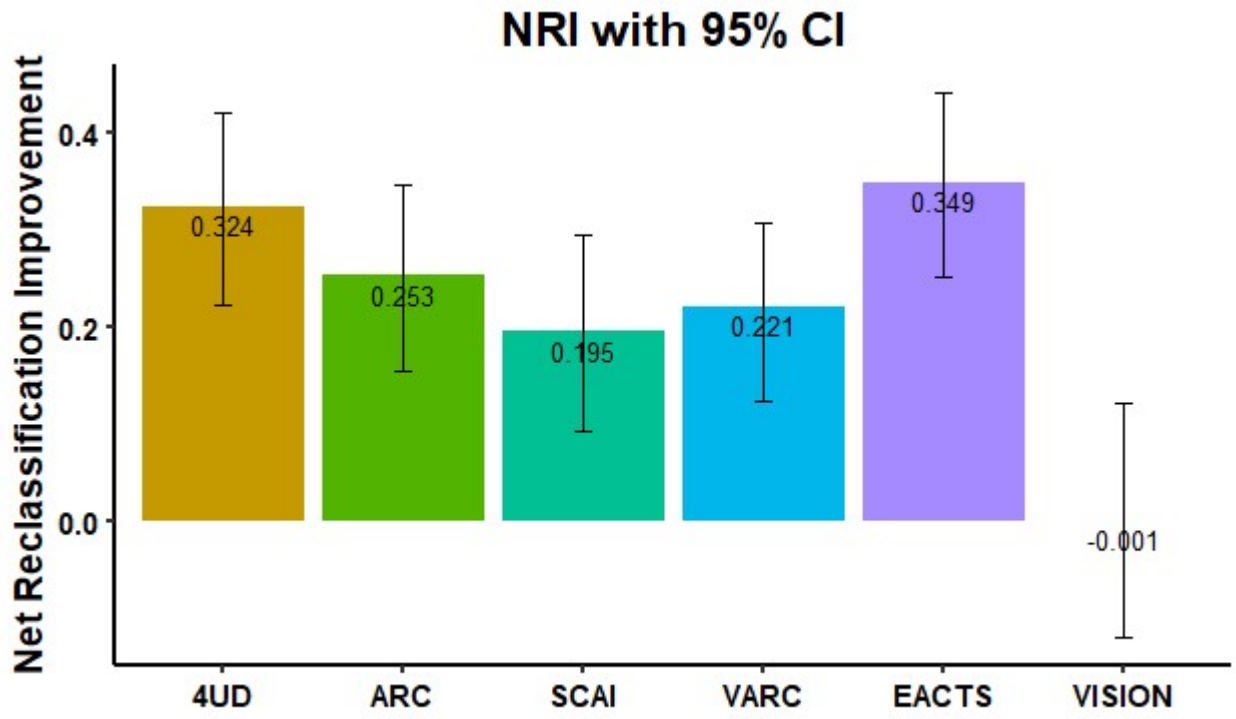



The likelihood ratio test results show the chi-square statistics for each pMI criterion, indicating the incremental value added to the baseline model for predicting 1-year mortality.

pMI: perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

In NRI and IDI analyses, both 4UD and EACTS criteria were superior in improving patient risk reclassification and discrimination. 4UD shows an NRI of 0.324 and an IDI of 0.0063, while EACTS shows an NRI of 0.349 and an IDI of 0.0055 (Figures 11 and 12). It should be noted that the VISION criteria showed no significant improvement in either NRI or IDI.

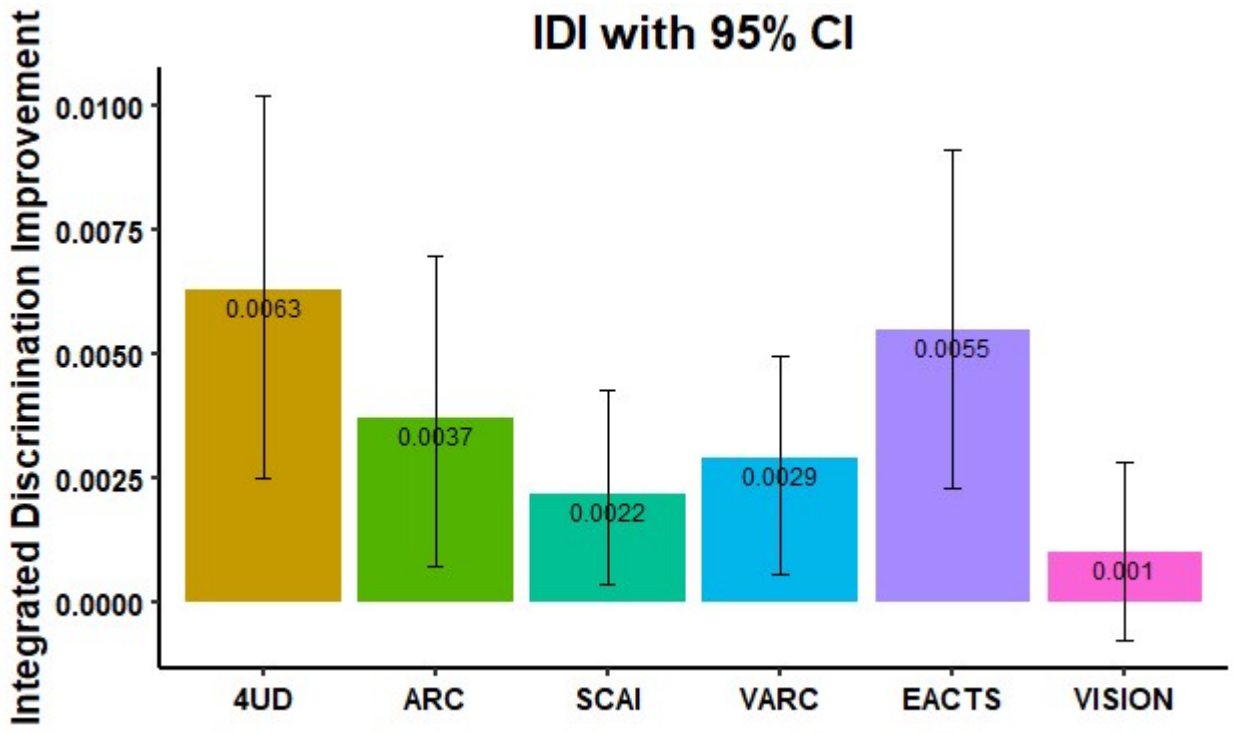
**Figure 11. Net Reclassification Improvement with 95% Confidence Intervals**




NRI values for each pMI criteria are presented with their 95% CI.

NRI: Net Reclassification Improvement, CI: confidence interval, pMI: Perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

**Figure 12. Integrated Discrimination Improvement with 95% Confidence Intervals**




The IDI values for each pMI criteria are presented with their 95% CI.

IDI: Integrated Discrimination Improvement, CI: Confidence Interval, pMI: Perioperative Myocardial Infarction, 4UD: 4th Universal Definition of Myocardial Infarction, ARC: Academic Research Consortium, SCAI: Society for Cardiovascular Angiography and Interventions, VARC: Valve Academic Research Consortium, EACTS, European Association of Cardio-Thoracic Surgery, VISION: Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

***Sensitivity analyses***

According to sensitivity analyses, which included data from the recent ten years and modified the baseline EuroSCORE II model with surgical factors such as off-pump CABG and surgical duration, the results were consistent with the primary analysis. The VISION criteria remained the most predictive for operative mortality, while the 4UD and EACTS criteria were most effective for predicting 1-year mortality. Detailed results of these sensitivity analyses are provided in the Supplementary Results.

**Discussion**

This study evaluated various definitions of pMI following CABG to determine their prognostic value for operative and 1-year all-cause mortality. The VISION criteria were the most predictive of operative mortality, a short-term outcome. On the other hand, the 4UD and EACTS criteria showed better accuracy in predicting 1-year mortality, demonstrating a superior ability to predict long-term outcomes.

In CABG, it has been proposed that pMI is caused by several mechanisms of myocardial injury.[2-4] Inadequate myocardial protection, ischemia-reperfusion injury, distal microembolization, and/or surgical manipulation-induced trauma can lead to myocardial injury. Furthermore, graft-related factors such as incomplete revascularization, graft occlusion, or spasm also have an impact. Additionally, perioperative hemodynamic instability and oxygen supply-demand mismatches can contribute to myocardial injury. This myocardial injury can lead to clinical signs including new ECG abnormalities such as Q waves or left bundle branch block, and regional wall motion abnormality. It is highly plausible that these myocardial injuries and resulting clinical signs are related to poor patient outcomes. In this regard, various pMI criteria have been developed to include these elements, combining biomarker increases with clinical signs to diagnose pMI. However, it is uncertain which criteria are most effective in predicting outcomes both in short-term and long-term prognosis. Our study addresses this gap by evaluating different pMI criteria and their predictive ability for postoperative short-term and long-term mortality. As a result, we observed noticeable differences in the predictive ability of pMI definitions for short-term and long-term outcomes, since some criteria offer distinct advantages depending on the prognostic timeframe. This variation may be explained by the differences in biomarker cut-offs and the mandatory inclusion of clinical signs within each diagnostic criteria.

For operative mortality, VISION myocardial injury was identified to be the most predictive. This definition is based solely on extremely high troponin levels, establishing thresholds significantly higher than other definitions. The strength of VISION is that it specifically derived a biomarker

threshold from CABG patients, unlike other diagnostic criteria which did not.[2,5,9] Indeed, CABG patients have a higher degree of baseline myocardial injury than those undergoing non-cardiac surgery or percutaneous coronary intervention.[9,12,13] For this reason, there have been concerns regarding the troponin threshold for previous pMI criteria, which were arbitrarily set based on percutaneous coronary intervention criteria.[14-16] In VISION, a high troponin threshold derived from CABG patients ensures that only severe postoperative myocardial injuries are classified as significant. Since VISION exhibited the best ability to predict operative death when compared to other diagnostic criteria, the severe subtype of myocardial injury may have a greater impact on postoperative short-term outcomes. Furthermore, other studies have suggested higher thresholds as high as 130-500 times UNL, demonstrating a significant relationship between highly elevated troponin levels and short-term outcomes with such elevated troponin levels.[15,17,18] Altogether, the use of criteria with a high threshold for cardiac biomarkers may be useful to identify patients at high risk of immediate postoperative death, emphasizing the significance of severe myocardial injuries in immediate postoperative outcomes.

In contrast, the 4UD and EACTS criteria were the most effective predictors of long-term mortality. These criteria are characterized by their relatively low troponin threshold (10 times the upper normal limit) and the requirement for clinical signs. Due to the lower threshold, most CABG patients would meet the biomarker criteria. Although ARC is similar, it employs a higher troponin cut-off (35 times the UNL), making it slightly more stringent regarding troponin elevations. Considering this, diagnostic criteria encompassing a larger proportion of patients with clinical signs appear to be more effective at predicting long-term mortality. Notably, VISION, which focuses solely on severe biomarker elevation without clinical signs, was among the least predictive of long-term mortality. Moreover, the SCAI and VARC criteria include a biomarker-only pathway, potentially weakening their predictive power by including patients without clinical signs. A biomarker-only pathway is also included in the EACTS criteria, but with a very high threshold (500 times the upper normal limit). Hence, EACTS may minimize biomarker only pathway's impact on prediction accuracy. According to

previous studies regarding long-term outcomes, criteria that incorporate ischemic signs are significantly more predictive of long-term outcomes than those without ischemic signs.[19-21] Furthermore, although isolated postoperative high troponin levels are associated with postoperative 30-day mortality, their prognostic significance weakens over a five-year period following surgery.[17] In this regard, ischemic signs may be a crucial predictor of long-term survival as they may indicate a vulnerable heart to myocardial damage, and criteria that emphasize ischemic signs rather than postoperative biomarker elevation may be appropriate to predict long-term survival.

***Limitation***

This study has several limitations. First, it was conducted at a single center with a predominantly Asian population, which may limit the generalizability of the findings to other populations. Second, the long study period may introduce temporal biases due to changes in surgical techniques and perioperative care over time. Finally, the use of insurance data for mortality outcomes restricts our ability to distinguish between cardiac and non-cardiac deaths, which is particularly relevant as cardiac death would be a more reliable outcome measure.

**Conclusions**

In this observational study, the VISION criteria were the most effective for predicting immediate postoperative mortality, while the 4UD and EACTS criteria were superior for predicting 1-year mortality. These findings suggest the importance of selecting appropriate pMI and perioperative myocardial injury criteria based on the specific prognostic timeframe and clinical context.

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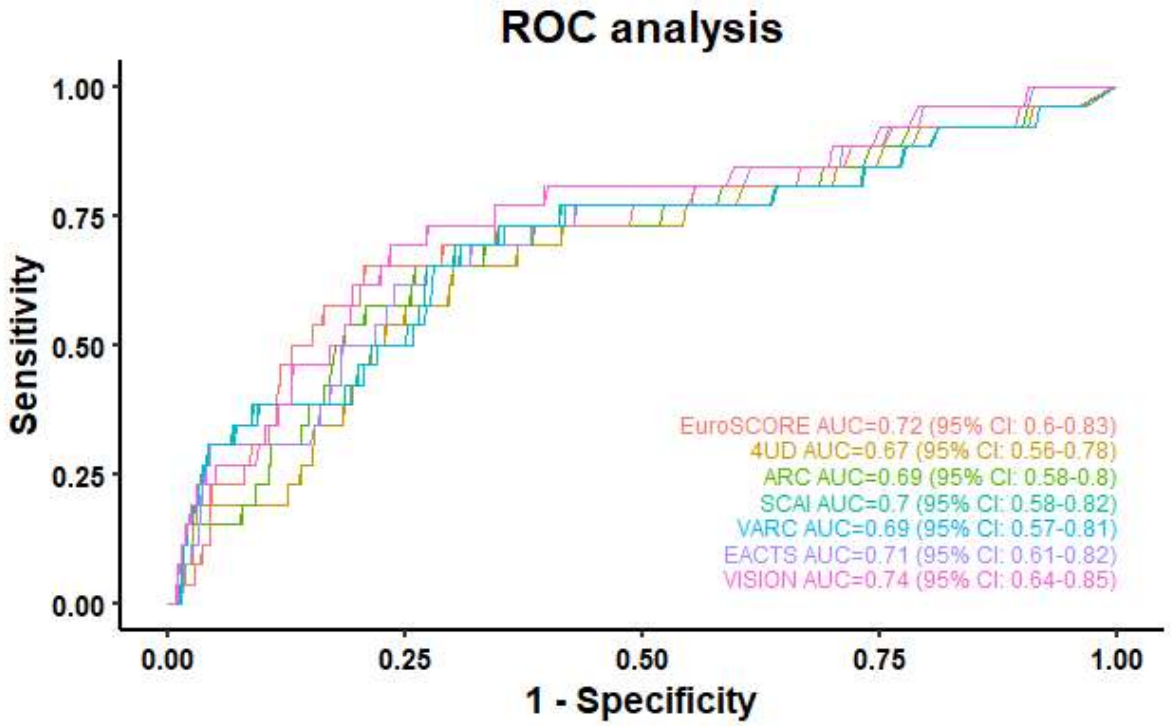
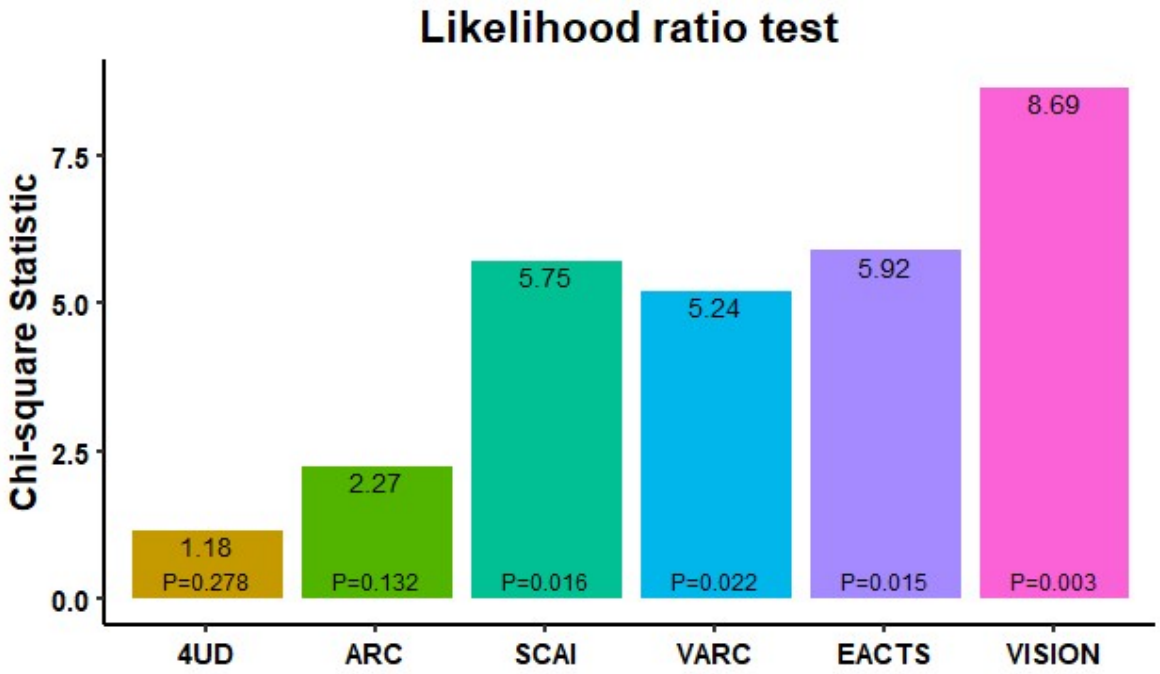
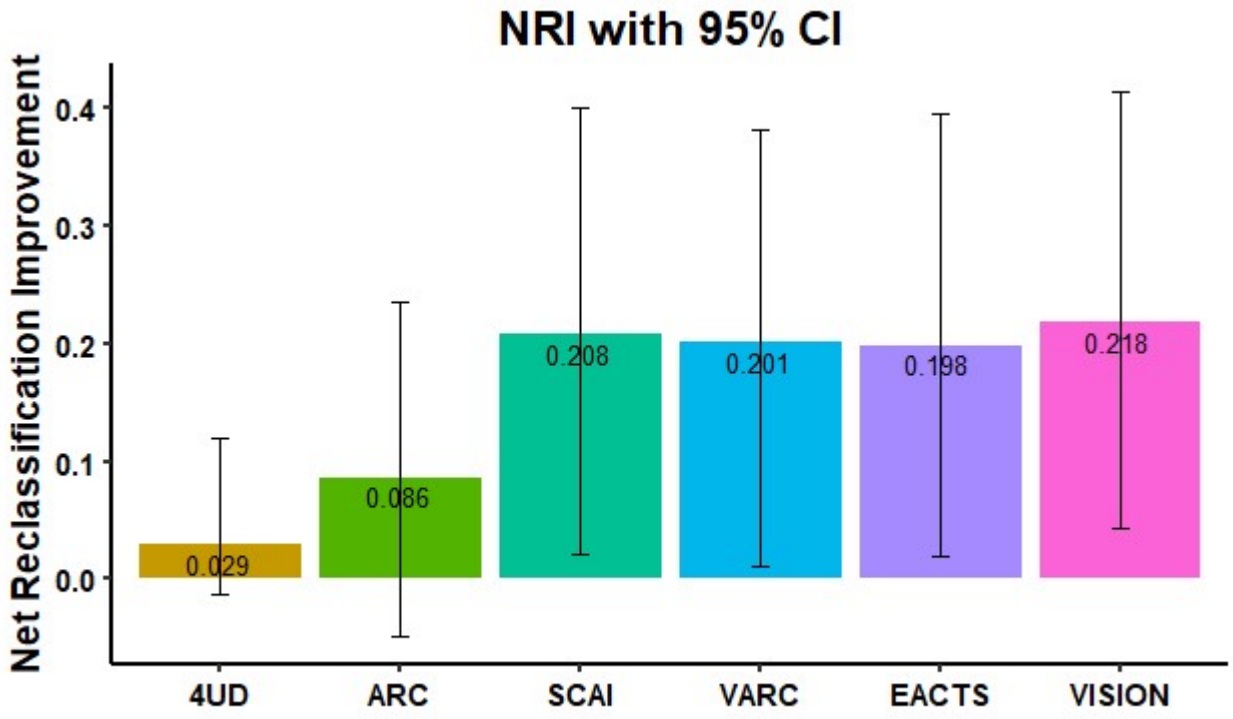
**Supplementary Results**

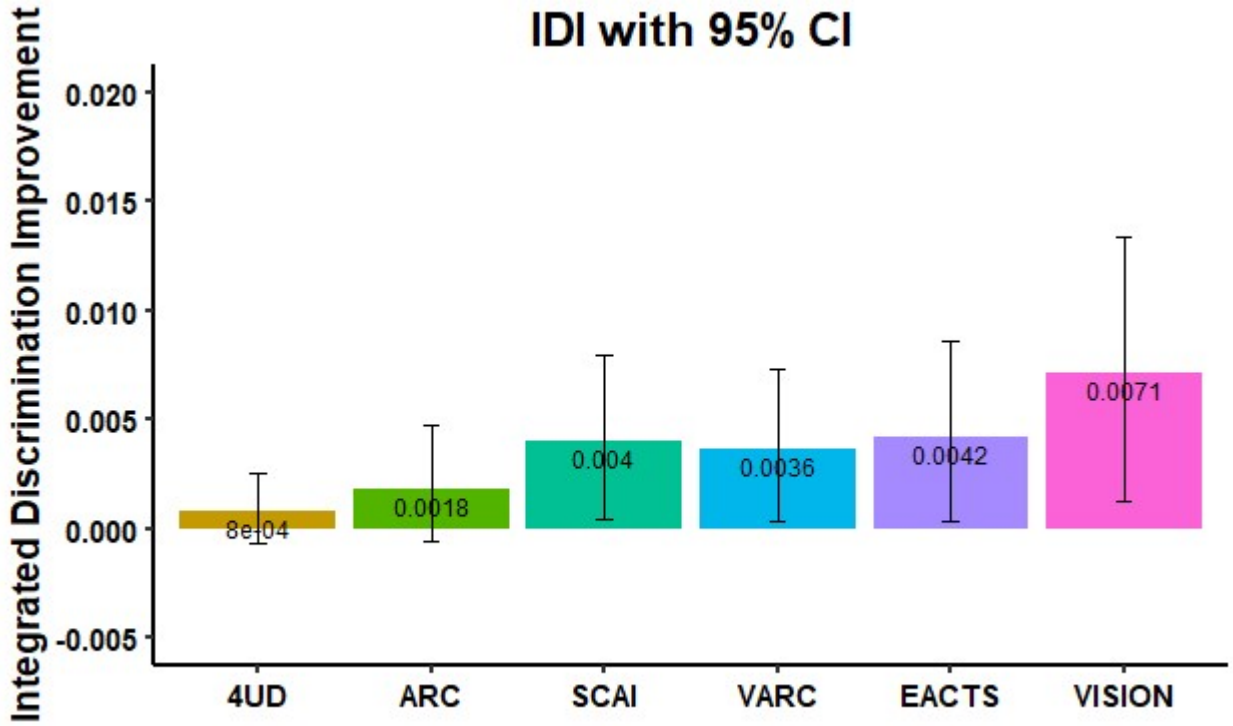
***Sensitivity analysis 1. data from the most recent ten years***

***Operative death***

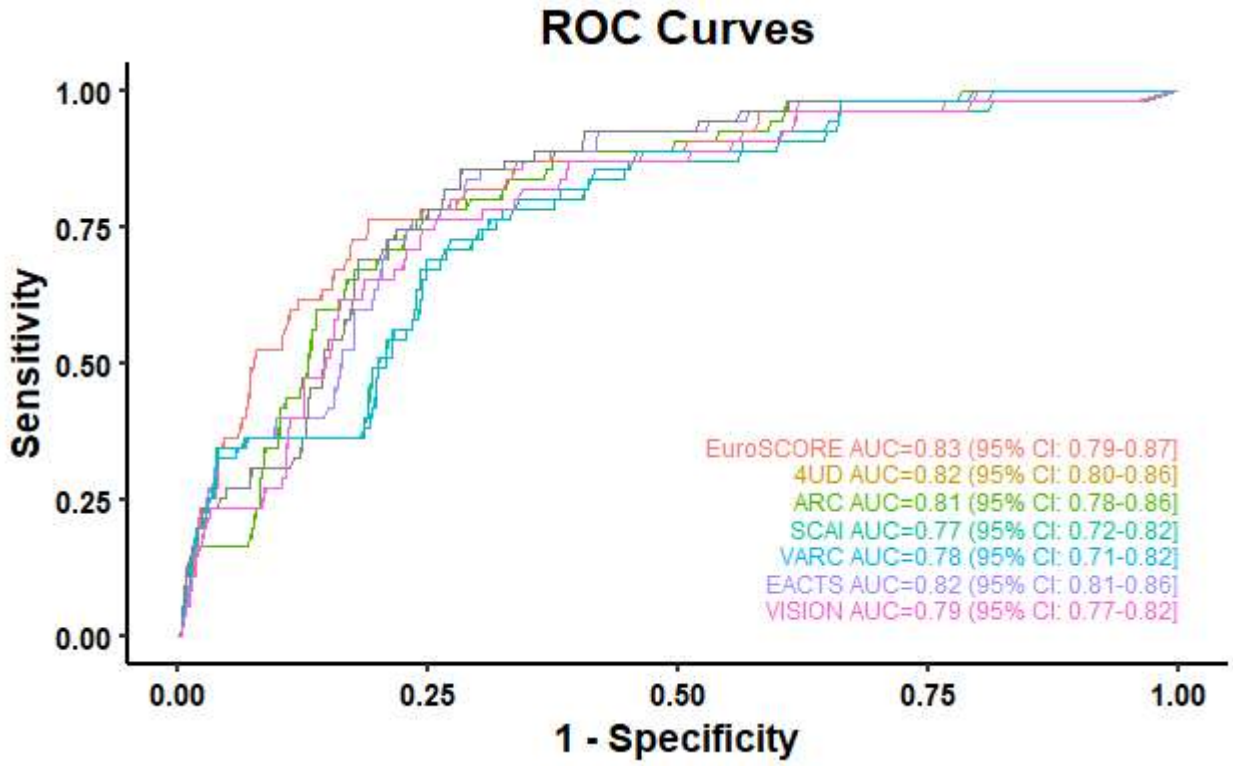


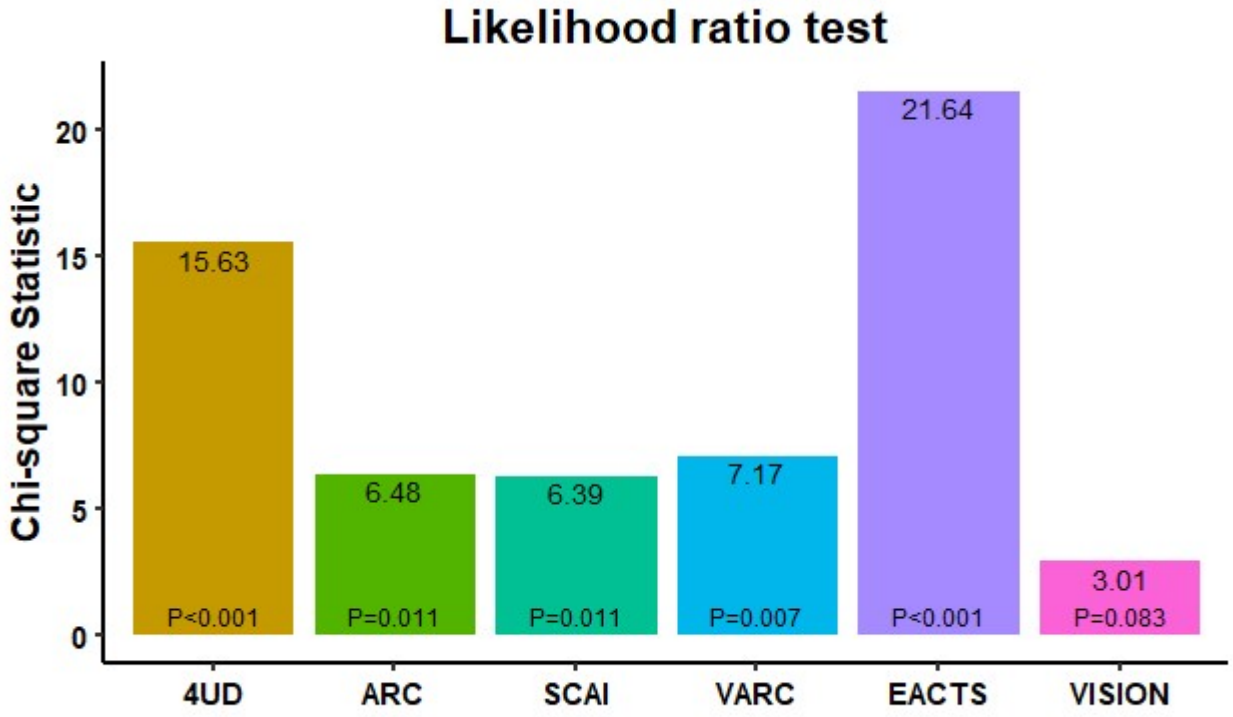



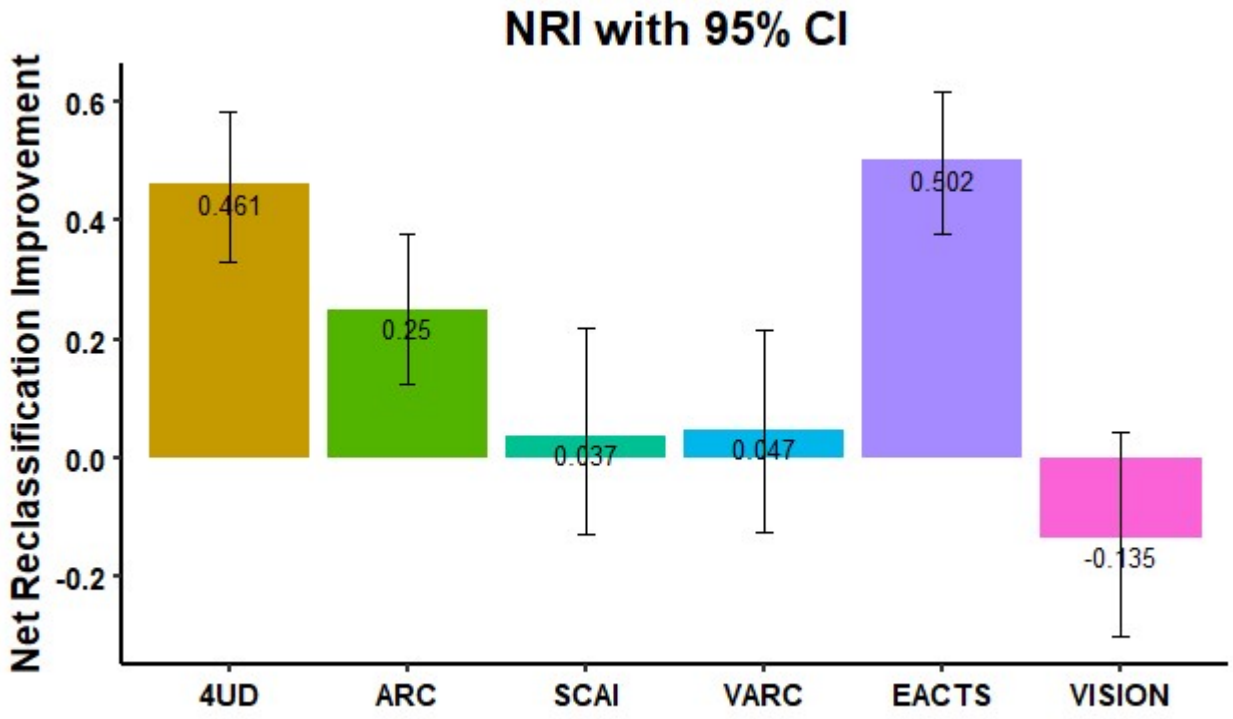


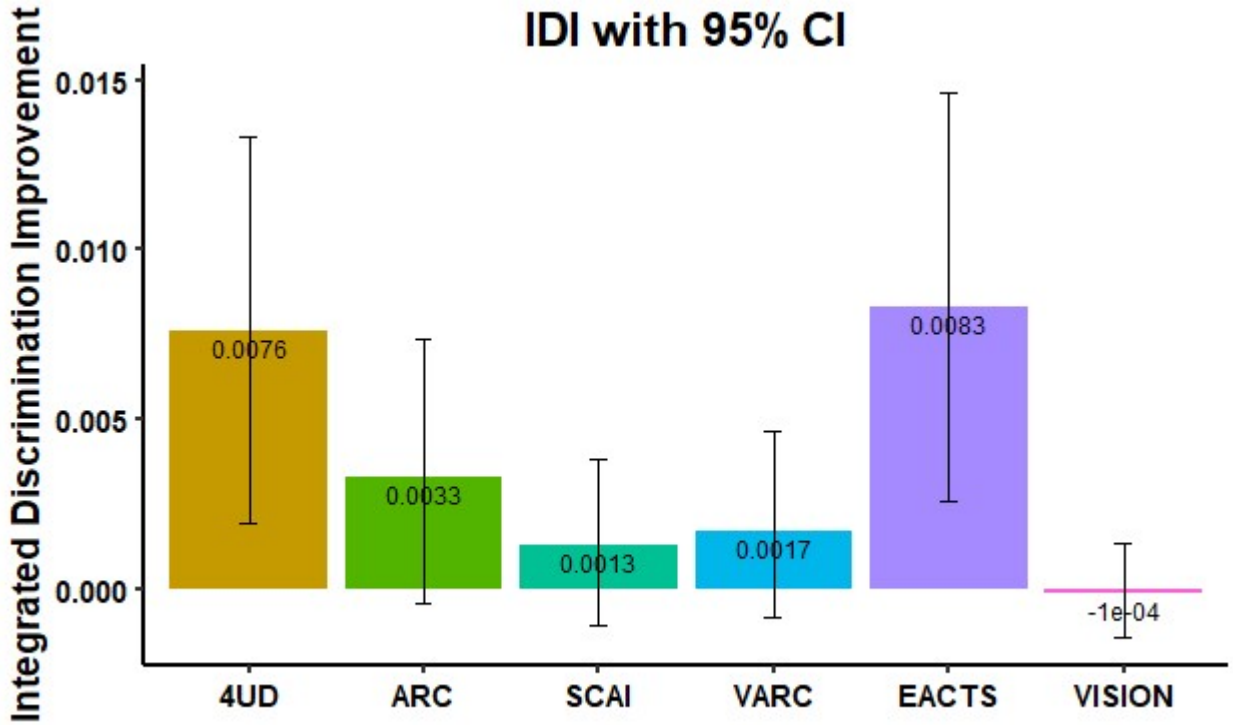



***Postoperative 1-year death***



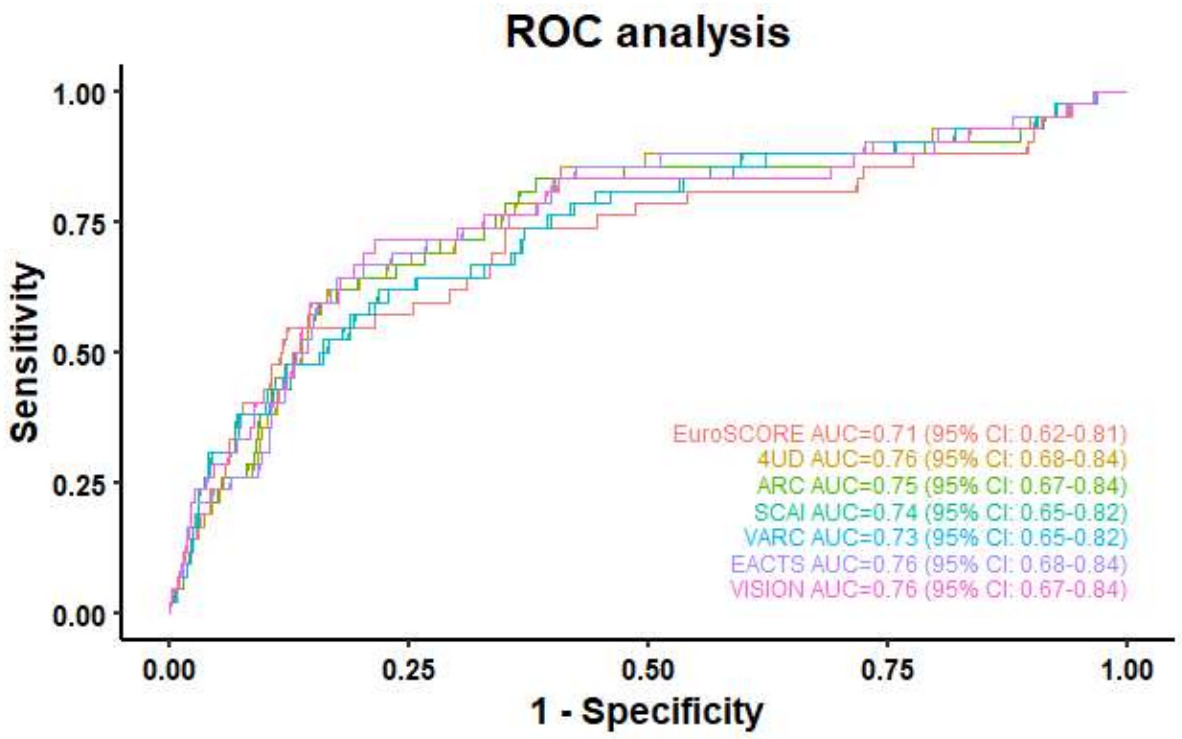



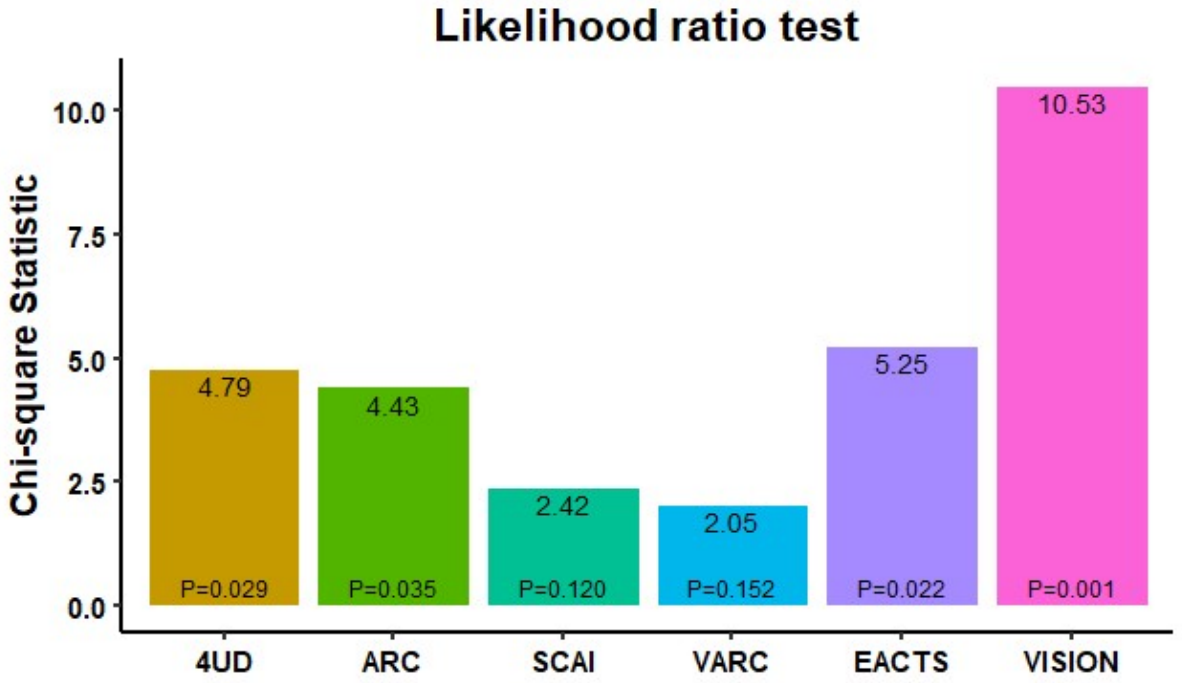


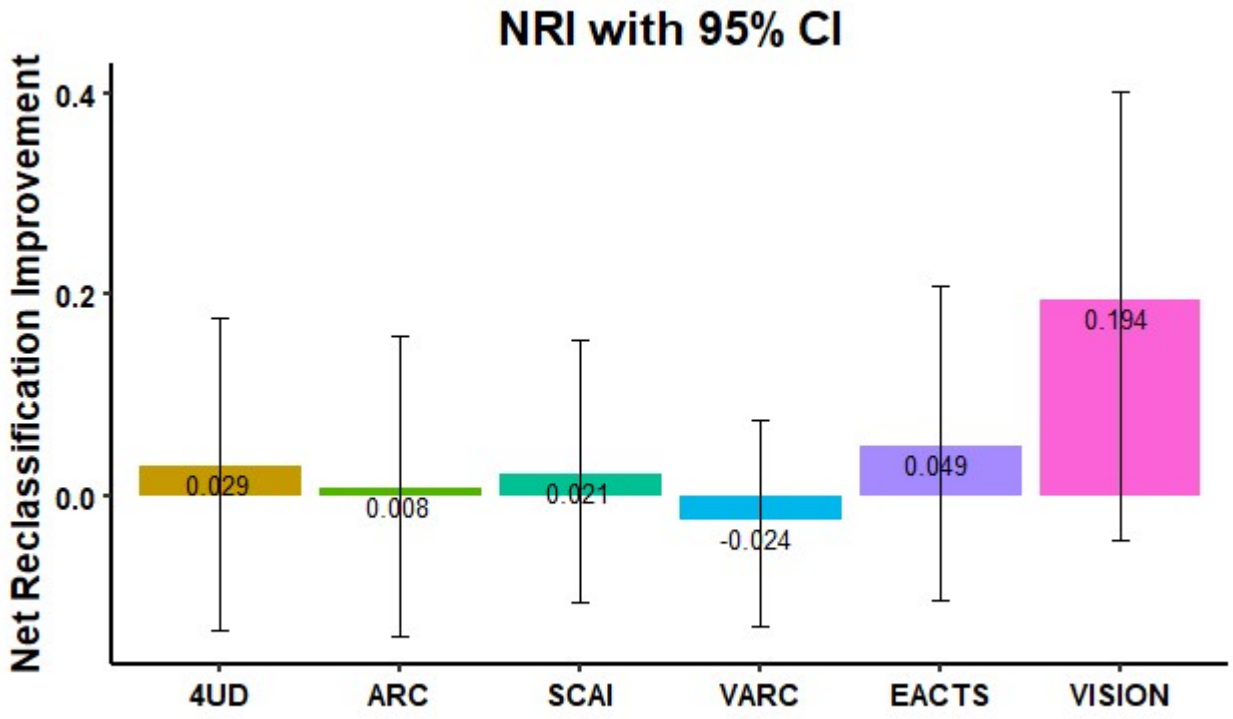



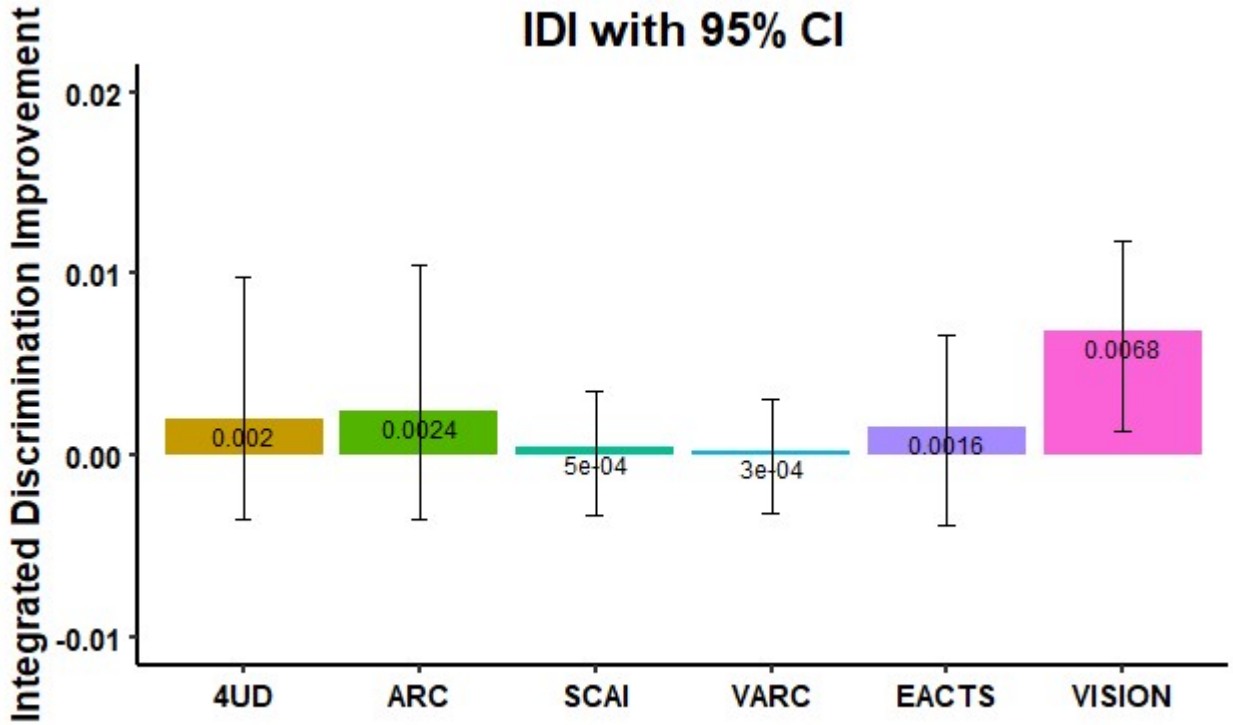
***Sensitivity analysis 2. surgical factors such as off-pump CABG and surgical duration added to EuroSCORE II***

***Operative death***

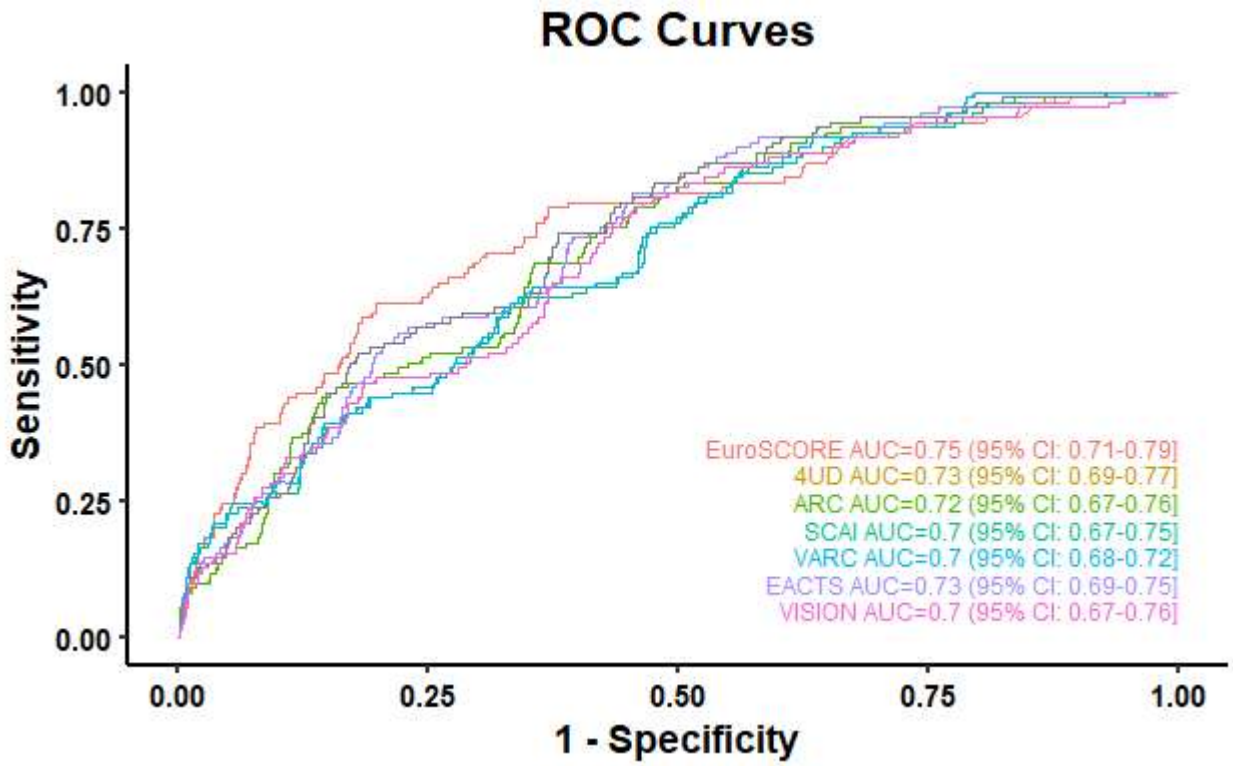


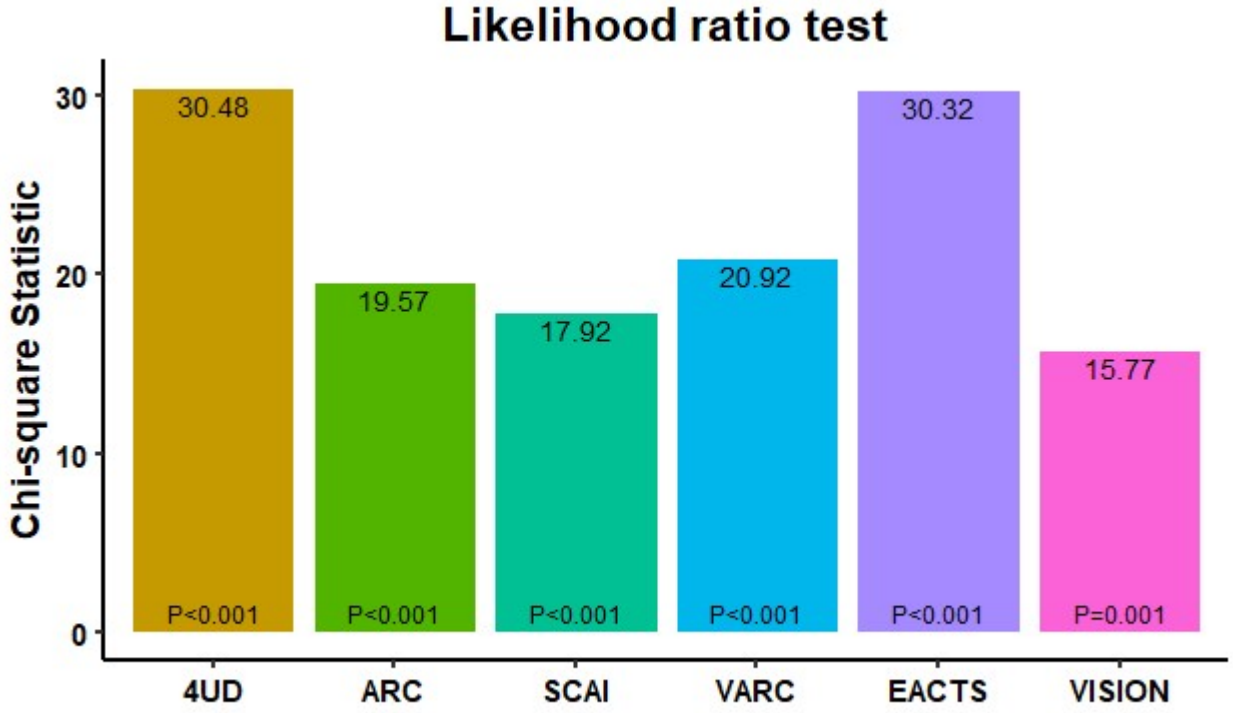



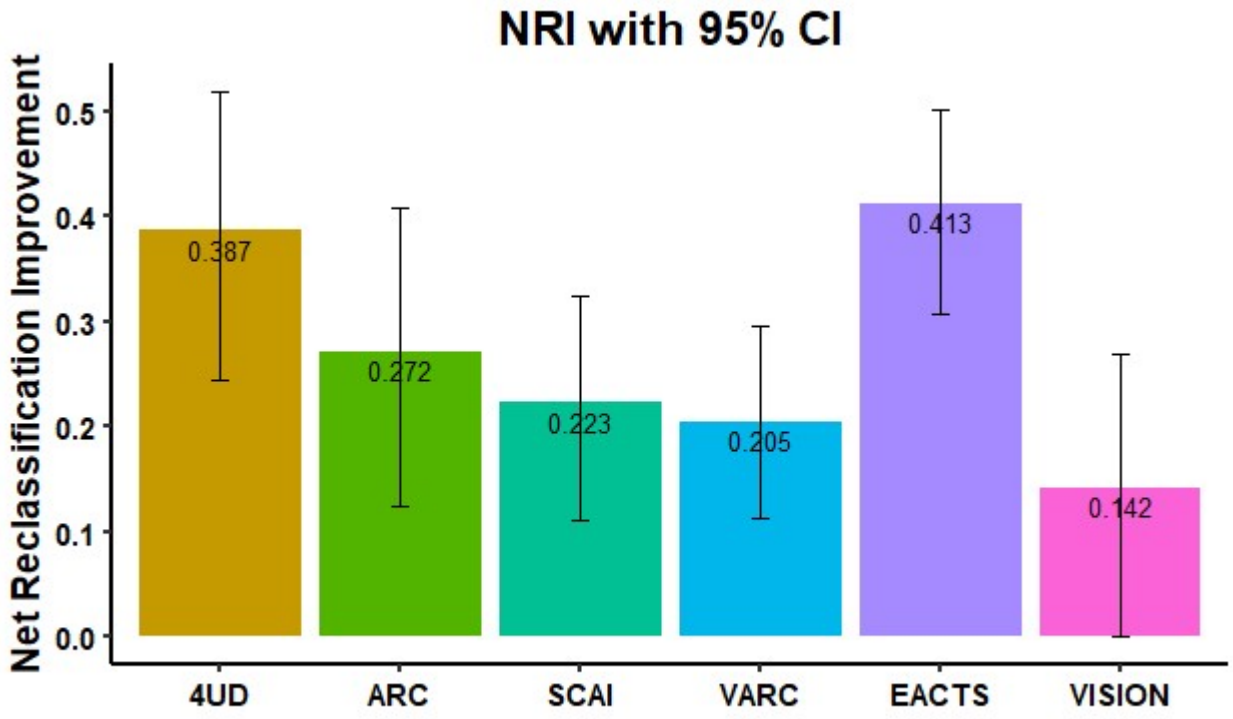


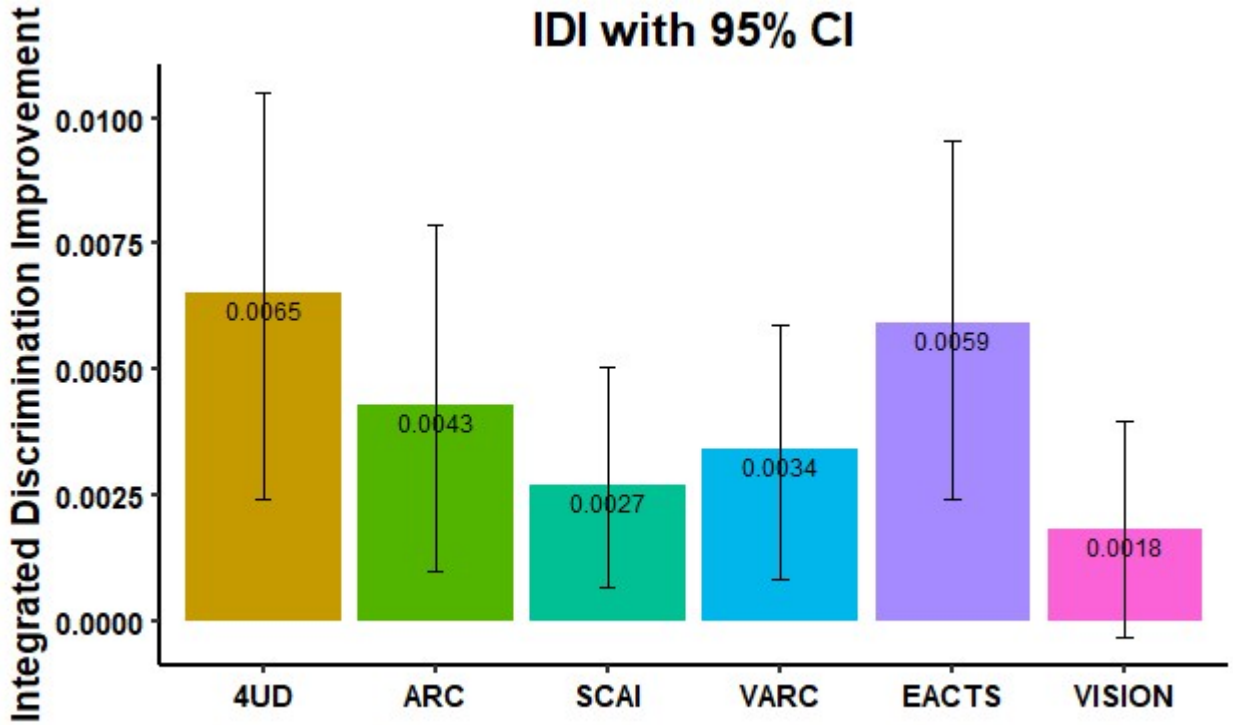



***Postoperative 1-year death***





## 국문요약

### 연구배경

관상동맥우회술 후 perioperative myocardial infarction (pMI)의 정의는 다양하지만, 어떤 정의가 예후와 가장 관련성이 높은지는 명확하지 않다. 본 연구의 목적은 (i) 다양한 pMI 정의와 수술 후 사망률 간의 연관성을 조사하고 (ii) 수술 후 사망률 예측에 있어 가장 큰 가치를 가지는 정의를 확인하는 것이다.

### 방법

한국의 단일 3차 병원에서 정규 관상동맥우회술을 받은 3,211명의 환자를 대상으로 코호트 연구를 진행하였다. 다음 여섯 가지 다른 pMI 정의에 따라 수술 후 심근경색의 예후 가치를 평가했다: (i) the 4th Universal Definition of Myocardial Infarction (4UD), (ii) the Academic Research Consortium (ARC), (iii) the Society for Cardiovascular Angiography and Interventions (SCAI), (iv) the Valve Academic Research Consortium (VARC), (v) the European Association of Cardio-Thoracic Surgery (EACTS), (vi) the Vascular Events in Surgery Patients Cohort Evaluation (VISION) Cardiac Surgery study criteria. 연구의 공동 주요 결과는 수술 사망률(수술 후 30일 이내의 모든 원인 사망 또는 퇴원 전 사망)과 수술 후 1년 모든 원인 사망률이었다. 각 정의의 추가 예후 가치는 the area under the receiver operating characteristic curve (AUC), likelihood ratio tests, net reclassification improvement (NRI), integrated discrimination improvement (IDI)를 사용하여 평가했다.

### 결과

수술 사망률은 1.3% (3,211명 중 42명)였고, 1년 사망률은 3.4% (3,211명 중 109명)였다. VISION myocardial injury criteria는 수술 사망률과 가장 강한 독립적 연관성을 보였다 [odds ratio (OR) 5.27; 95% confidence interval (CI) 2.84 to 9.79; 4UD: OR 3.49; 95% CI 1.47 to 5.74; ARC: OR 3.49; 95% CI 1.70 to 7.20; SCAI: OR 2.54; 95% CI 1.38 to 4.67; VARC: OR 2.43; 95% CI 1.32 to 4.49; EACTS: OR 3.29; 95% CI 1.75 to 6.19]. VISION criteria는 수술 사망률 예측에 가장 높은 추가 가치를 가졌다 (AUC 0.78; Chi-square statistic 24.19; NRI 0.325; IDI 0.0116). 반면, 4UD는 1년 사망률과 가장 강한 연관성을 보였다 [hazard ratio (HR) 3.29; 95% confidence interval (CI) 2.18

to 4.97; ARC: HR 2.92; 95% CI 1.83 to 4.67; SCAI: HR 2.16; 95% CI 1.48 to 3.15; VARC: HR 2.32; 95% CI 1.60 to 3.38; EACTS: HR 3.09; 95% CI 2.08 to 4.58; VISION: HR 2.25; 95% CI 1.47 to 3.44]. 4UD와 EACTS criteria는 1년 사망률 예측에 있어 가장 의미 있는 추가 가치를 보여주었다 (4UD: AUC 0.77, Chi-square statistic 26.91, NRI 0.324, IDI 0.0063; EACTS: AUC 0.76, Chi-square statistic 27.37, NRI 0.349, IDI 0.0055).

**결론**

관상동맥우회술 후 다양한 pMI 정의 중 VISION myocardial injury criteria가 수술 사망률 예측에 가장 큰 추가 가치를 제공하며, 4UD와 EACTS definitions of Myocardial Infarction이 1년 모든 원인 사망률 예측에 가장 효과적이다.