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기관내 수술 건수를 반영한 심장 수술 후 사망률 예측모델 구축

Institutional case volume incorporated mortality risk prediction model after cardiac surgery

2021년 8월

서울대학교 대학원

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Abstract

Institutional case volume incorporated mortality risk prediction model after cardiac surgery

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Although several studies suggest that higher case volume correlates with low mortality after coronary artery bypass grafting surgery (CABG), the association between case volume and patient outcome requires a re-evaluation as most studies do not reflect recent advances in CABG. In addition, most risk prediction models predicting short-term mortality after cardiac surgery incorporate patient characteristics, laboratory data, and type of surgery, but do not account for surgical experience. Considering the importance of case volume on postoperative outcome after cardiac surgery, the novel mortality prediction model incorporating case

volume could be needed. The aim of this study was to compare survival after CABG according to the institutional annual CABG case volume and attempt to develop a risk prediction model for mortality after cardiac surgery that incorporates institutional case volume.

Adult patients (≥ 18 years) who underwent CABG from 2009 to 2016 were identified by searching National Health Insurance database of Korea for CABG procedure codes. Hospitals were classified into 3 groups based on annual case volume: low-volume centers (< 20 cases/year), medium-volume centers (20-50 cases/year), and high-volume centers (> 50 cases/year) for evaluation. After that, adult patients who underwent all cardiac surgery from 2009 to 2016 were also identified. Patients who underwent cardiac surgery (n=57,804) were randomly divided into the derivation cohort (n=28,902) or the validation cohorts (n=28,902). A risk prediction model for in-hospital mortality and 1-year mortality was developed from the derivation cohort and the performance of the model was evaluated in the validation cohort.

The overall 1-year mortality rate after CABG was the lowest in high-volume centers (6.5%), followed by medium-volume centers (10.6%) and low-volume centers (15.2%). Logistic regression identified medium-volume centers (adjusted OR 1.30 [95% CI 1.15-1.49], $P < 0.01$) and low-volume centers (adjusted OR 1.75 [95% CI 1.51-2.03], $P < 0.01$) as risk factors for 1-year mortality after CABG compared to high-volume centers. In the Cox proportional hazard model, low- and medium-volume centers was significantly risk factors for poor survival (adjusted HR 1.41 [95% CI 1.31-1.54], $P < 0.01$ and HR 1.26 [95% CI 1.17-1.35], $P < 0.01$ for low- and medium-volume centers, respectively). In addition, the novel

implemented mortality prediction model demonstrated fair discrimination (c-statistics, 0.76 for in-hospital mortality in both cohorts; 0.74 for 1-year mortality in both cohorts) and acceptable calibration. Hospitals were classified based on case volume into 50 or less, 50-100, 100-200, or more than 200 average cardiac surgery cases per year and case volume was a significant variable in the prediction model.

In conclusion, higher institutional case volume of CABG was still associated with better postoperative outcomes including in-hospital mortality and mid-term mortality compared to institutions with low or medium case volume, even with advances in surgery and technology. Furthermore, considering the importance of case volume on postoperative outcome after cardiac surgery, the novel mortality prediction model incorporating case volume could be needed. Therefore, this study showed the newly developed and validated risk prediction model for in hospital and 1-year mortality after cardiac surgery with good discrimination and calibration. The model may provide risk prediction for patients undergoing cardiac surgery using baseline characteristics, type of surgery, and hospital case volume.

Keywords : Case volume, Cardiac surgery, Mortality, Prediction model
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1. Introduction

The European System for Cardiac Operative Risk Evaluation (EuroSCORE), EuroSCORE II and The Society of Thoracic Surgeons (STS) score are cardiac surgery risk models for predicting mortality after cardiac surgery, derived either from an international European or US database of cardiac surgical patients.[1-5] Although improved from Euroscore,[2] EuroSCORE II still shows room for improvement in predicting mortality in high-risk patients.[6,7] The STS score, suggested to be superior to EuroSCORE in predicting cardiac surgery risk,[8,9] also seem to lack accuracy in high-risk patients. Both models do not provide long-term prognosis after cardiac surgery.

The relationship between surgical case volume and patient's outcome has been demonstrated across various, complex surgical procedures.[10-12] Similar relationships have been shown in cardiac surgery such as coronary artery bypass graft surgery (CABG)[13] and valve surgery.[14,15] Although most studies suggest that higher case volume correlates with low mortality,[16-18] the association between case volume and patient outcome requires a re-evaluation as most studies do not reflect recent advances in CABG. Moreover, previous reports focused on short-term mortality rather than mid-term or long-term impacts of case volume on outcomes after CABG.[17,18] Therefore, these findings raise clinical and investigational questions: would previous studies explain the relationship between case volume and postoperative outcome, reflecting current technological advances on CABG which contribute to a decrease in mortality? In addition, despite the relationship between case volume and mortality, institutional case volume, which can be considered as a measure of perioperative performance has not been incorporated into mortality prediction models after cardiac surgery. Cardiac surgery risk models that do not incorporate case volume cannot be expected to reflect surgical expertise that improves with accumulating experience.

Therefore, in this study, I evaluated the association between institutional annual CABG case volume and mortality after CABG, including mid-term mortality. Furthermore, the aim of this study was ultimately to develop a new mortality prediction model composed of baseline patient characteristics, type of surgery, and institutional cardiac surgical volume.

2. Study methods

This study was a retrospective cohort study. The study protocol was exempted from review by the institutional review board of Seoul National University Hospital due to the feasibility. The National Healthcare Insurance Service (NHIS) in South Korea is a single-payer universal healthcare system, which covers 97% of the population in Korea.[19] The NHIS database is provided to researchers after de-identifying personal information for research purposes and contains demographic information, diagnostic code using ICD-10 (International Classification of Diseases) codes, NHI procedure code, and all prescription medications dispensed.

2.1 Coronary artery bypass grafting surgery case volume and mid-term mortality

Adult patients (18 years or older) who underwent CABG from January 2009 to December 2016 were identified by searching NHI procedure codes for CABG. Baseline patient characteristics and risk factors in patients undergoing CABG were listed in Table 1. Types of the CABG were classified into off-pump or on-pump and single or multiple anastomosis. The institutional case-volume was defined as the average annual number of CABG including on-pump CABG and off-pump CABG performed during the study period. Centers were then categorized into 3 groups according to annual case-volume; high-volume centers (> 50 cases/year), medium-volume centers (20-50 cases/year) and low-volume centers (< 20 cases/year). The primary outcome was 1-year mortality after CABG in relation to the annual CABG case volume of the center. In-hospital mortality, 3- and 5-year mortality after

CABG was also evaluated.

Table 1. Definitions of the risk factor using ICD-10 codes and/or NHI procedure codes used for evaluation of effect of case volume on mortality after coronary artery bypass grafting surgery.

Risk factors	**Definition**
Hypertension	I10-I15
Diabetes mellitus	E10- E14
Hyperlipidemia	E7
End stage renal disease	N1 with NHI procedure code for dialysis
Extracardiac arteriopathy	I65.2, I70.0, I70.2, I73.9, I74.1-5
Cerebrovascular disease	I60-I69
Chronic lung disease	J40-J47, J849, J8418
Pulmonary hypertension	I27.0, I27.2
Congestive heart failure	I11.0, I50.0
Cardiogenic shock	R57.0
Previous cardiac arrest	I46, I46.0, I46.1, I46.9
Atrial fibrillation	I48
Sustained Vfib, VT	I47.2, I49.0
History of percutaneous coronary intervention	NHI procedure code
Myocardial infarction	I21.0, I21.1, I21.2, I21.3, I21.4, I21.9
Non-Myocardial infarction, coronary artery disease	I20.0
Emergency surgery	NHI procedure code for anesthesia for emergency procedure
Off-pump CABG	OA641, OA642, OA647
Number of distal anastomosis (2or more)	O1641, OA641

Transfusion	NHI procedure code for transfusion

ICD, International Classification of Diseases; NHI, National Healthcare Insurance Service; Vfib, ventricular fibrillation; VT, ventricular tachycardia

2.2 Patients population for development of novel mortality prediction model

Adult patients (age≥18) who underwent cardiac surgery from January 2009 to December 2016 by searching NHI procedure codes were identified. NHI procedure codes included all types of cardiac surgery. Underlying risk factors were extracted from the database using ICD-10 codes and/or NHI procedure codes (Table 2). If a patient is admitted to another hospital within two days after being discharged from a hospital due to cardiac surgery, the same hospitalization due to cardiac surgery was defined to assess in-hospital mortality. In-hospital mortality was identified based on the information at discharge and patient mortality was determined when NHI healthcare coverage was terminated due to death; this was processed when the patient's death certificate was automatically reported to the NHIS.

Table 2. Definitions of the risk factor using ICD-10 codes and/or NHI procedure codes used for novel mortality prediction model after cardiac surgery.

Risk factors	**Definition**
Hypertension	I10-I15
Diabetes mellitus	E10- E14
Hyperlipidemia	E7
Chronic lung disease	J40-J47, J849, J8418
End stage renal disease	N1 with NHI procedure code for dialysis

Myocardial infarction within 3 months	I21.0, I21.1, I21.2, I21.3, I21.4, I21.9
History of percutaneous coronary intervention	NHI procedure code
Unstable angina	I20.0
Congestive heart failure	I11.0, I50.0
Atrial fibrillation	I48
Arrhythmia other than atrial fibrillation	R57.0, I46, I46.0, I46.1, I46.9, I47.2, I49.0, I44.0, I44.1, I44.2, I44.3
Transfusion	NHI procedure code for transfusion
Emergency surgery	NHI procedure code for anesthesia for emergency procedure

ICD, International Classification of Diseases; NHI, National Healthcare Insurance Service.

2.3 Risk factors and model development

Prediction models for in-hospital mortality and 1-year mortality after cardiac surgery were developed and validated. Conventional cardiovascular risk factors included in EuroSCORE or STS score, such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, end stage renal disease, chronic lung disease, myocardial infarction (MI) within the past 3 months, history of percutaneous coronary intervention (PCI), unstable angina, congestive heart failure, atrial fibrillation, arrhythmia other than atrial fibrillation, and emergency procedures were collected (Table 2). Additionally, the amount of perioperative packed red blood cell transfusion and cardiac surgery case volume in each hospital per year were also collected. Other risk factors such as end stage renal disease, chronic lung disease, history of PCI, unstable angina, congestive heart failure, and arrhythmia were collected from the medical records and reimbursement data one year before surgery. Hypertension was defined as ICD codes for hypertension with anti-hypertensive drug prescribed for more than 1 month. Diabetes mellitus was defined both ICD code for diabetes and insulin or oral hypoglycemic agent prescribed for more than 1 month. Hyperlipidemia was defined as ICD code for hyperlipidemia with lipid-lowering medications prescribed for more than 3 months. Emergency surgical procedures were identified by searching general anesthesia codes for emergency procedures. Cardiac surgery type was classified into valve surgery, CABG, surgery on thoracic aorta, combined surgery, and reoperation. Combined surgery was defined as two or more types of cardiac surgery (ex: concomitant CABG and aortic valve replacement) performed in the same hospitalization period. Similarly, reoperation was determined when patients received the same type of surgery more than once (ex: mitral valve replacement revision after mitral valve replacement) during the same hospitalization period. Institutions were classified according to their average annual case volume. The cut-offs for classifying centers into case volume groups were determined after considering the distribution of centers and the number of patients in each group. Potential prediction models were developed using baseline patient characteristics and risk factors listed in Table 2. Institutional case volume was also considered for the models. Prediction models were compared to select a model with the best discrimination and calibration.

2.4 Statistical analysis

Risk factors for mortality after CABG were evaluated using multivariate logistic regression model which adjusted for various relevant factors (Table 1). Survival after CABG was compared using Cox proportional hazard model after adjusting for relevant risk factors. Kaplan-Meier survival curves were generated, and log-rank test was performed for comparison.

Half of the cardiac surgery cohort was randomly divided into the derivation cohort for development of risk prediction models and the remaining 50% of cardiac surgery patients were included in the validation cohort. Using the derivation cohort, in-hospital mortality and 1-year mortality prediction models after cardiac surgery were developed using multivariable logistic regression models. Factors such as patient characteristics, type of surgery, and case volume were considered based on literature reviews and clinical expert opinion and selected using the univariable analysis and the likelihood ratio test. The performance of each mortality prediction model was tested with the validation cohort. The c-statistic for prediction model was used to evaluate the ability of each model in discriminating patients who died in the hospital after cardiac surgery and within 1 year thereafter.[20] Observed risk and predicted risk of each outcome were compared by ranking participants into deciles of predicted risk. The calibration (how closely the prediction reflects an actual event) of each model was evaluated in the validation cohort using both Hosmer-Lemeshow test and the ratio of observed and predicted probabilities. The calibration was presented using the ratio of observed and predicted probabilities because large sample size is often cited as the reason for significant Hosmer-Lemeshow. Additionally, the risk prediction models for in-hospital and 1-year mortality were translated into a simple score system, similar to EuroSCORE or STS score. The formula of the risk prediction model was

$$\text{Predicted mortality} = \frac{e^{(\beta_0 + \sum \beta_i X_i)}}{1 + e^{(\beta_0 + \sum \beta_i X_i)}}$$

where e was the base of the natural logarithm and is approximately 2.718. β_0 were the constant of the logistic regression model, -4.4963 and -3.9651 for in-hospital and 1-year mortality, respectively. β_i were the coefficients of the variable X_i in the logistic regression model and X_i were the dummy variables for the categorical risk factors.

The reference values were assigned for each category of each risk factor in the risk prediction model to indicate that less healthy risk factor had positive points so that a higher point score conveys more risk. Points associated with each category of each risk factor were computed by $\mathrm{Points}_{ij} = \beta_i(W_{ij} - W_{iREF})/B$, where β_i were the regression coefficients for each of the i risk factor, W_{ij} were the reference value (values 0 or 1 for risk factors modelled using dummy variables) for the jth category of the ith risk factor, W_{iREF} were the reference value of the reference category of the ith risk factor, and B was the constant that reflect 1 point in the final points system. The one point was considered to be equivalent to the increase in risk associated with age group 50-59 in both risk prediction models.[21]

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, USA). P values less than 0.05 were considered statistically significant. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, USA). Two-sided values of $p < 0.05$ were considered statistically significant.

3. Study results

3.1 Annual case volume after coronary artery bypass grafting surgery and mortality.

A total of 22,575 CABG were performed in 95 centers between 2009 and 2016 in Korea. Patient characteristics are shown in Table 3. High volume centers (15 centers) performed 14,697 (65.1%) CABG cases during the study period, while medium volume centers (26 centers) and low volume centers (54 centers) performed 5,262 (23.3%) and 2,616 (11.6%) CABG cases, respectively.

The overall 1-year mortality rate after CABG was 8.5% (1,912/22,575). The 1-year mortality was 6.5% (957/14,697) in high-volume centers, 10.6% (557/5,262) in medium-volume centers, and 15.2% (398/2,616) in low-volume centers. The 3-year mortality in high-, medium-, and low-volume centers were 12.1%, 17.2%, and 20.0%, respectively. Similar trends were demonstrated in in-hospital mortality (2.9%, 5.8%, and 10.1% in high-, medium-, and low-volume centers, respectively) and 5-year mortality (16.9%, 24.2%, and 25.2% in high-, medium-, and low-volume centers, respectively). The inverse correlation between annual CABG case-volume and mortality after CABG for each center were shown in Figure. 1.

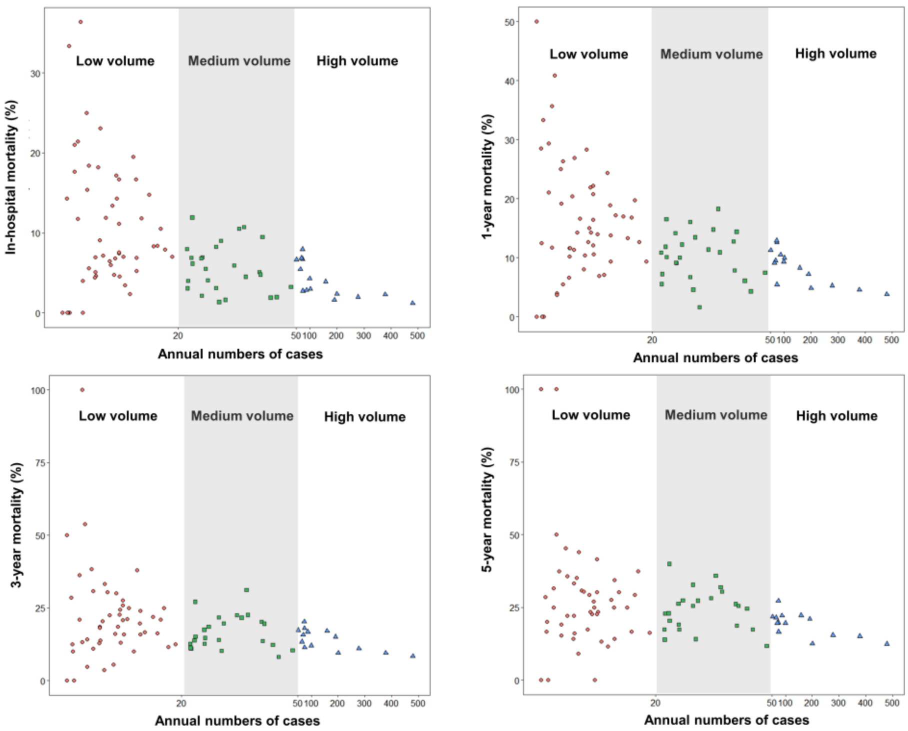


Figure 1. Case-volume and all mortality after coronary artery bypass grafting surgery

Table 3. Patient characteristics according to annual case volume in patients undergoing coronary artery bypass grafting surgery.

Variables	Overall	Low volume center (<20 cases/year)	Medium volume center (20-50 cases/year)	High volume center (>50 cases/year)	P value
Number of patients	22,575 (100%)	2,616 (11.6%)	5,262 (23.3%)	14,697 (65.1%)	
Number of centers	95 (100%)	54 (56.8%)	26 (27.4%)	15 (15.8%)	
Age (years)	66.1± 9.9	65.6 ± 9.9	66.4± 9.8	66.0± 10.0	<0.01
Female	5,912 (26.2%)	785 (30.0%)	1,440 (27.4%)	3,687 (25.1%)	<0.01
Pre-existing comorbidity					
Hypertension	15,543 (68.9%)	1,769 (67.6%)	3,494 (66.4%)	10,280 (70.0%)	<0.01
Diabetes mellitus	8,737 (38.7%)	1,035 (39.6%)	2,053 (39.0%)	5,649 (38.4%)	0.48
Hyperlipidemia	9,143 (40.5%)	1,022 (39.1%)	2,208 (38.5%)	6,093 (41.5%)	<0.01
End stage renal disease	654 (2.9%)	105 (4.0%)	120 (2.3%)	429 (2.9%)	<0.01
Extracardiac arteriopathy	4,544 (20.1%)	536 (20.5%)	1,121 (21.3%)	2,887 (19.6%)	0.03
Cerebrovascular disease	4,699 (20.8%)	499 (19.1%)	1,152 (21.9%)	3,048 (20.7%)	0.01
Chronic lung disease	7,454 (33.0%)	857 (32.8%)	1,809% (34.4%)	4,788 (32.6%)	0.06
Pulmonary hypertension	13 (0.1%)	2 (0.1%)	3 (0.1%)	8 (0.1%)	0.91
Congestive heart failure	2,918 (12.9%)	347 (13.3%)	731 (13.9%)	1,840 (12.5%)	0.03
Cardiogenic shock	31 (0.1%)	6 (0.2%)	6 (0.1%)	19 (0.1%)	0.39
Previous cardiac arrest	52 (0.2%)	6 (0.2%)	8 (0.2%)	38 (0.3%)	0.38
Atrial fibrillation	876 (3.9%)	109 (4.2%)	179 (3.4%)	588 (4.0%)	0.11
Sustained Vfib, VT	74 (0.3%)	8 (0.3%)	19 (0.4%)	46 (0.3%)	0.86

Previous PCI	1,537 (6.8%)	193 (7.4%)	306 (5.8%)	1,038 (7.1%)	<0.01
Diagnosis					<0.01
Myocardial infarction (MI)	2,268 (10.1%)	278 (10.6%)	523 (9.9%)	1,467 (10.0%)	
Non-MI, CAD	14,343 (63.5%)	1,481 (56.6%)	3,087 (58.7%)	9,775 (66.5%)	
Unspecified	5,964 (26.4%)	857 (32.8%)	1,652 (31.4%)	3,455 (23.5%)	
Emergency surgery	278 (1.2%)	52 (2.0%)	101 (1.9%)	125 (0.9%)	<0.01
Off-pump CABG	13,758 (60.9%)	888 (33.9%)	1,562 (29.7%)	11,308 (76.9%)	<0.01
Previous CABG	311 (1.4%)	70 (2.7%)	73 (1.4%)	168 (1.1%)	
Number of distal anastomosis					
1	2,158 (9.6%)	454 (17.4%)	629 (12.0%)	1,075 (7.3%)	
2 or more	20,106 (89.1%)	2,092 (80.0%)	4,560 (86.7%)	13,454 (91.5%)	
Perioperative RBC transfusion	2.8±2.1 (2[2-3])	3.4±2.3 (3[2-4])	3.0±2.1 (3[2-4])	2.6±2.0 (2[1-3])	<0.01

Data are presented as mean (SD), median [IQR], or number (%). Abbreviations: CABG, coronary artery bypass grafting surgery; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; RBC, red blood cell; Vfib, ventricular fibrillation; VT, ventricular tachycardia

3.2 Logistic regression analysis and cox proportional hazard model for mid-term mortality in patients undergoing coronary artery bypass grafting surgery.

Logistic regression identified medium-volume centers (adjusted OR 1.30 [95% CI 1.15-1.49], $P < 0.01$) and low-volume centers (adjusted OR 1.75 [95% CI 1.51-2.03], $P < 0.01$) as risk factors for 1-year mortality after CABG compared to high-volume centers (Table 4). Compared to high-volume centers, low-volume centers (adjusted OR 1.44 [95% CI 1.24-1.67], $P < 0.01$) and medium-volume centers (adjusted OR 1.31 [95% CI 1.16-1.48], $P < 0.01$) showed significantly higher 3-year mortality after adjusting various cardiovascular risk factors (Table 4). This study also showed a similar trend in in-hospital mortality (adjusted OR 2.23 [95% CI 1.84-2.69], $P < 0.01$ in low-volume centers vs high-volume centers.) and 5-year mortality (adjusted OR 1.43 [95% CI 1.21-1.69], $P < 0.01$ in low-volume centers vs high-volume centers.) after CABG. The smaller the case volume, the higher the mortality was identified (Table 4). In addition, off-pump CABG tends to reduce short term mortality or long term mortality compared to on-pump CABG and redo CABG surgery seems to increase mortality risk (Table 4).

Table 4. Multivariable regression analysis for mortality after coronary artery bypass grafting surgery

	In-hospital mortality		1-year mortality		3-year mortality		5-year mortality	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Case volume								
High volume center	Reference		Reference		Reference		Reference	
Medium volume center	1.42 (1.19, 1.69)	<0.01	1.30 (1.15, 1.49)	<0.01	1.31 (1.16, 1.48)	<0.01	1.36 (1.19, 1.56)	<0.01
Low volume center	2.23 (1.84, 2.69)	<0.01	1.75 (1.51, 2.03)	<0.01	1.44 (1.24, 1.67)	<0.01	1.43 (1.21, 1.69)	<0.01
Age (years)								
18-49	Reference		Reference		Reference		Reference	
50-59	1.24 (0.74, 2.06)	0.42	1.20 (0.83, 1.74)	0.34	1.24 (0.88, 1.74)	0.22	1.27 (0.89, 1.82)	0.19
60-69	1.94 (1.19, 3.15)	<0.01	1.98 (1.39, 2.82)	<0.01	2.21 (1.60, 3.06)	<0.01	2.40 (1.71, 3.39)	<0.01
70-79	3.43 (2.12, 5.55)	<0.01	3.89 (2.73, 5.50)	<0.01	4.16 (3.02, 5.73)	<0.01	4.63 (3.30, 6.51)	<0.01
>80	7.12 (4.30, 11.79)	<0.01	8.40 (5.82, 12.14)	<0.01	9.24 (6.54, 13.04)	<0.01	12.3 (8.46, 17.88)	<0.01
Female	0.90 (0.77, 1.06)	0.20	0.77 (0.69, 0.87)	<0.01	0.69 (0.62, 0.77)	<0.01	0.79 (0.61, 0.77)	<0.01
Pre-existing comorbidity								
Hypertension	0.99 (0.83, 1.19)	0.94	1.19 (1.04, 1.36)	0.01	1.27 (1.12, 1.44)	<0.01	1.14 (0.97, 1.30)	0.06
Diabetes mellitus	0.98 (0.84, 1.14)	0.79	1.05 (0.94, 1.17)	0.38	1.13 (1.23, 1.25)	0.02	1.32 (1.18, 1.47)	<0.01
Hyperlipidemia	1.00 (0.86, 1.17)	1.00	0.95 (0.85, 1.07)	0.40	0.96 (0.86, 1.07)	0.46	0.99 (0.89, 1.11)	0.90
End stage renal disease	1.18 (1.39, 2.44)	<0.01	2.15 (1.72, 2.68)	<0.01	3.89 (3.07, 4.94)	<0.01	6.45 (4.77, 8.71)	<0.01
Extracardiac arteriopathy	0.93 (0.78, 1.11)	0.43	1.11 (0.98, 1.26)	0.10	1.09 (0.97, 1.23)	0.14	1.04 (0.91, 1.18)	0.59
Cerebrovascular disease	0.99 (0.83, 1.17)	0.86	1.01 (0.89, 1.14)	0.88	1.12 (1.00, 1.26)	0.06	1.26 (1.12, 1.43)	<0.01

Chronic lung disease	0.97 (0.83, 1.12)	0.64	1.07 (0.96, 1.19)	0.24	1.09 (0.99, 1.21)	0.10	1.13 (1.02, 1.27)	0.02
Congestive heart failure	1.22 (1.00, 1.48)	0.05	1.26 (1.09, 1.45)	<0.01	1.38 (1.20, 1.58)	<0.01	1.57 (1.35, 1.82)	<0.01
Atrial fibrillation	1.28 (0.95, 1.74)	0.11	1.57 (1.26, 1.95)	<0.01	1.67 (1.35, 2.06)	<0.01	1.50 (1.18, 1.91)	<0.01
Previous PCI	0.97 (0.71, 1.32)	0.83	10.92 (0.73, 1.15)	0.46	0.85 (0.69, 1.06)	0.15	0.99 (0.79, 1.25)	0.95
Diagnosis								
MI	Reference		Reference		Reference		Reference	
Non-MI, CAD	0.97 (0.76, 1.25)	0.82	0.79 (0.66, 0.95)	0.01	0.76 (0.64, 0.89)	<0.01	0.82 (0.69, 0.98)	0.03
Unspecified	1.20 (0.91, 1.58)	0.19	1.24 (1.02, 1.51)	0.03	1.22 (1.01, 1.47)	0.04	1.38 (1.13, 1.69)	<0.01
Emergency surgery	2.34 (1.60, 3.44)	<0.01	1.82 (1.29, 2.56)	<0.01	1.47 (1.03, 2.10)	0.03	1.41 (0.95, 2.08)	0.09-
Off-pump CABG	0.57 (0.49, 0.67)	<0.01	0.71 (0.63, 0.79)	<0.01	0.87 (0.78, 0.098)	0.02	0.88 (0.78, 0.99)	0.03
Number of distal anastomosis								
1	Reference		Reference		Reference		Reference	
2 or more	2.20 (1.78, 2.71)	<0.01	1.87 (1.60, 2.20)	<0.01	1.60 (1.37, 1.88)	<0.01	1.50 (1.25, 1.80)	<0.01
Previous CABG	1.03 (0.63, 1.68)	0.90	1.24 (0.86, 1.80)	0.26	1.13 (0.78, 1.63)	0.52	1.07 (0.72, 1.59)	0.75
Surgery year	0.97 (0.94, 1.00)	0.03	0.98 (0.95, 1.00)	0.03	1.02 (0.99, 1.05)	0.25	1.01 (0.97, 1.06)	0.55
Perioperative RBC transfusion								
0-1 units	Reference		Reference		Reference		Reference	
2-3 units	2.97 (1.90, 4.64)	<0.01	1.46 (1.20, 1.78)	<0.01	1.28 (1.09, 1.50)	<0.01	1.29 (1.10, 1.50)	<0.01
4-5 units	11.7 (7.55, 18.3)	<0.01	4.2 (3.38, 5.12)	<0.01	3.2 (2.72, 3.84)	<0.01	2.5 (2.11, 3.01)	<0.01
≥6 units	55.1 (35.4, 85.8)	<0.01	15.3 (12.3, 18.9)	<0.01	9.9 (8.17, 12.0)	<0.01	8.0 (6.48, 9.92)	<0.01

Abbreviations: CABG, Coronary artery bypass grafting surgery; CAD, Coronary artery disease; CI, confidence interval; MI, Myocardial infarction; OR, odds ratio; PCI, Percutaneous coronary intervention; RBC, Red blood cell.

Table 5. Cox proportional hazard model for mortality after coronary artery bypass grafting surgery

	Univariate analysis		Multivariate analysis	
	Crude hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
Case volume				
High volume center	Reference		Reference	
Medium volume center	1.40 (1.31, 1.49)	<0.01	1.26 (1.17, 1.35)	<0.01
Low volume center	1.69 (1.57, 1.83)	<0.01	1.41 (1.31, 1.54)	<0.01
Age (years)				
18-49	Reference		Reference	
50-59	1.50 (1.22, 1.84)	<0.01	1.34 (1.09, 1.65)	<0.01
60-69	2.38 (1.96, 2.89)	<0.01	2.16 (1.78, 2.63)	<0.01
70-79	4.42 (3.65, 5.35)	<0.01	3.95 (3.25, 4.80)	<0.01
>80	9.23 (7.55, 11.29)	<0.01	8.01 (6.53, 9.83)	<0.01
Female	1.02 (0.96, 1.09)	0.50	0.70 (0.65, 0.74)	<0.01
Pre-existing comorbidity				
Hypertension	1.53 (1.43, 1.63)	<0.01	1.17 (1.09, 1.26)	<0.01
Diabetes mellitus	1.37 (1.30, 1.45)	<0.01	1.27 (1.20, 1.34)	<0.01
Hyperlipidemia	1.08 (1.03, 1.15)	<0.01	1.00 (0.95, 1.06)	0.95
End stage renal disease	4.23 (3.81, 4.69)	<0.01	2.98 (2.67, 3.33)	<0.01
Extracardiac arteriopathy	1.40 (1.32, 1.49)	<0.01	1.07 (1.00, 1.15)	0.03
Cerebrovascular disease	1.49 (1.41, 1.59)	<0.01	1.13 (1.06, 1.20)	<0.01
Chronic lung disease	1.39 (1.32, 1.47)	<0.01	1.11 (1.05, 1.17)	<0.01

Congestive heart failure	1.70 (1.58, 1.82)	<0.01	1.35 (1.25, 1.46)	<0.01
Atrial fibrillation	1.88 (1.68, 2.01)	<0.01	1.57 (1.26, 1.95)	<0.01
Previous PCI	0.94 (0.85, 1.05)	0.29	0.90 (0.80, 1.01)	0.08
Diagnosis				
MI	Reference		Reference	
Non-MI,CAD	0.72 (0.66, 0.78)	<0.01	0.84 (0.77, 0.92)	<0.01
Unspecified	1.05 (0.96, 1.15)	0.33	1.28 (1.16, 1.41)	<0.01
Emergency surgery	1.73 (1.43, 2.01)	<0.01	1.48 (1.22, 1.79)	<0.01
Off-pump CABG	0.76 (0.72, 0.80)	<0.01	0.98 (0.92, 1.04)	0.45
Number of distal anastomosis				
1	Reference		Reference	
2 or more	1.39 (1.28, 1.52)	<0.01	1.37 (1.25, 1.49)	<0.01
Previous CABG	1.44 (1.19, 1.74)	<0.01	1.09 (0.89, 1.32)	0.41
Perioperative RBC transfusion				
0-1 units	Reference		Reference	
2-3 units	1.55 (1.42, 1.69)	<0.01	1.32 (1.20, 1.44)	<0.01
4-5 units	3.31 (3.01, 3.63)	<0.01	2.33 (2.11, 2.57)	<0.01
≥6 units	8.70 (7.87, 9.60)	<0.01	5.28 (4.75, 5.87)	<0.01

Abbreviations: CABG, Coronary artery bypass grafting surgery; CAD, Coronary artery disease; CI, confidence interval; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; RBC, Red blood cell.

In the Cox proportional hazard model, adjusted HRs were also higher in patients who underwent CABG in low- (adjusted HR 1.41 [95% CI 1.31-1.54], P < 0.01) and medium-volume centers (adjusted HR 1.26 [95% CI 1.17-1.35], P < 0.01) compared to high-volume centers (Table 5). Other clinical predictors for survival are shown in Table 5. As shown in Figure 2, long-term overall survival for up to 9 years after CABG was superior in high-volume centers (P < 0.01)

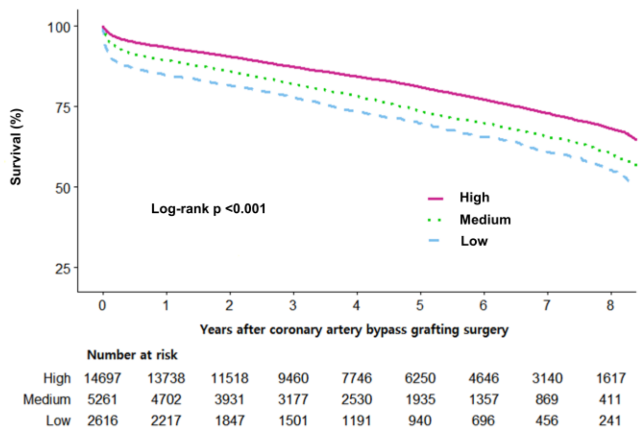


Figure 2. Kaplan-Meier survival curves according to case-volume.

3.3 Annual case volume after all cardiac surgery and mortality

Patients who underwent cardiac surgery (n=57,804) were randomly divided into the derivation cohort (n=28,902) or the validation cohorts (n=28,902). Patient characteristics of the derivation and validation cohorts are shown in Table 6. The distribution of potential risk factors after cardiac surgery were similar between the two cohorts. In-hospital mortality and 1-year mortality were 5.98% (3,457/57,804) and 9.78% (5,653/57,804), respectively. The distribution of a total of thirteen high-volume centers (≥ 200 cases per year) performed 37,350 (64.61%) cases of cardiac surgery during the study period, while the remaining centers with case volume of 50 or less, 50-100, 100-200 performed 11.90%, 12.78% and 10.70% cases of cardiac surgery, respectively. Patient and center characteristics according to case volume are shown in Table 7.

Table 6. Patient characteristics for total cohort, derivation cohort and validation cohort for novel model.

	Total cohort (N = 57,804)	Derivation cohort (N = 28,902)	Validation cohort (N = 28,902)	P
Age (median, IQR)	65 (55-73)	65 (55-73)	65 (55-73)	0.36
Age (years)				0.96
18-49	8,712 (15.07%)	4,375 (15.14%)	4,337 (15.01%)	
50-59	11,521 (19.93%)	5,783 (20.01%)	5,738 (19.85%)	
60-69	16,846 (29.14%)	8,389 (29.03%)	8,457 (29.26%)	
70-79	17,160 (29.69%)	8,579 (29.68%)	8,581 (29.69%)	
>80	3,565 (6.17%)	1,776 (6.14%)	1,789 (6.19%)	
Sex				0.95
Female	22,676 (39.23%)	11,342 (39.24%)	11,334 (39.22%)	
Male	35,128 (60.77%)	17,560 (60.76%)	17,568 (60.78%)	
End stage renal disease (receiving dialysis)	1,200 (2.08%)	581 (2.01%)	619 (2.14%)	0.27
Chronic lung disease	21,371 (36.97%)	10,672 (36.92%)	10,699 (37.02%)	0.82
Hypertension	36,953 (63.93%)	18,392 (63.64%)	18,561 (64.22%)	0.14
Hyperlipidemia	16,977 (29.37%)	8,369 (28.96%)	8,608 (29.78%)	0.03
Diabetes mellitus	13,071 (22.61%)	6,450 (22.32%)	6,621 (22.91%)	0.09
Myocardial infarction within 3 months	2,368 (4.10%)	1,215 (4.20%)	1,153 (3.99%)	0.19

Percutaneous coronary intervention	1,946 (3.37%)	947 (3.28%)	999 (3.46%)	0.23
Unstable angina	9,206 (15.93%)	4,626 (16.01%)	4,580 (15.85%)	0.60
Congestive heart failure	11,439 (19.79%)	5,732 (19.83%)	5,707 (19.75%)	0.79
Atrial fibrillation	9,125 (15.79%)	4,603 (15.93%)	4,522 (15.65%)	0.36
Arrhythmia other than atrial fibrillation	542 (0.94%)	260 (0.90%)	282 (0.98%)	0.34
RBC transfusion (median, IQR)	3 (2-4)	3 (2-4)	3 (2-4)	0.35
RBC Transfusion (units)				0.42
0-1 unit	10,650 (18.42%)	5,324 (18.42%)	5,326 (18.43%)	
2 units	17,078 (29.54%)	8,578 (29.68%)	8,500 (29.41%)	
3 units	13,311 (23.03%)	6,704 (23.30%)	6,607 (22.86%)	
≥4 units	16,765 (29.00%)	8,296 (28.70%)	8,469 (29.30%)	
Emergency surgery	1,175 (2.03%)	623 (2.16%)	552 (1.91%)	0.04
Type of surgery				0.97
Valve surgery	16,008 (27.69%)	8,013 (27.72%)	7,995 (27.66%)	
CABG	22,419 (38.78%)	11,172 (38.65%)	11,247 (38.91%)	
Re-operation[a]	9,533 (16.49%)	4,771 (16.51%)	4,762 (16.48%)	
Combined surgery[b]	7,142 (12.36%)	3,585 (12.40%)	3,557 (12.31%)	
Thoracic aorta surgery	2,702 (4.67%)	1,361 (4.71%)	1,341 (4.64%)	
Annual case volume				0.97
≥200	37,350 (64.61%)	18,668 (64.59%)	18,682 (64.64%)	
100 - 200	6,187 (10.70%)	3,110 (10.76%)	3,077 (10.65%)	

50 - 100	7,390 (12.78%)	3,697 (12.79%)	3,693 (12.78%)	
<50	6,877 (11.90%)	3,427 (11.86%)	3,450 (11.94%)	
Surgery year				0.82
2009-2011	20,808 (36.00%)	10,404 (36.00%)	10,404 (36.00%)	
2012-2014	20,606 (35.68%)	10,283 (35.58%)	10,343 (35.79%)	
2015-2016	16,370 (28.32%)	8,215 (28.42%)	8,155 (28.22%)	

Data are presented as mean (SD), median (IQR), or number (%).

RBC, red blood cells; CABG, coronary artery bypass grafting surgery.

[a] Re-operation was determined when patients received the same type of surgery more than once during the same hospitalization period.

[b] Combined surgery was defined as two or more types of cardiac surgery performed in the same hospitalization period.

Table 7. Patient characteristics according to annual case volume in all cardiac surgery.

	<50 cases / year	50-100 cases / year	100-200 cases / year	≥200 cases / year	P value
Number of cases	6,877 (11.90%)	7,390 (12.78%)	6,187 (10.70%)	37,350 (64.61%)	<0.01
Average annual number of cases	30.54	71.72	144.4	826.99	<0.01
Number of centers	58	18	9	13	
Age (years)	63.90 ± 12.25	64.65 ± 11.98	63.30 ± 12.65	62.17 ± 13.81	<0.01
18-49	851 (12.37%)	808 (10.93%)	846 (13.67%)	6,207 (16.62%)	
50-59	1,462 (21.26%)	1,395 (18.88%)	1,282 (20.72%)	7,382 (19.76%)	
60-69	1,971 (28.66%)	2,234 (30.23%)	1,808 (29.22%)	10,833 (29.00%)	
70-79	2,104 (30.59%)	2,458 (33.26%)	1,851 (29.92%)	10,747 (28.77%)	
>80	489 (7.11%)	495 (6.70%)	400 (6.47%)	2,181 (5.84%)	
Sex					0.03
Female	2,704 (39.32%)	2,895 (39.17%)	2,533 (40.94%)	14,544 (38.94%)	
Male	4,173 (60.68%)	4,495 (60.83%)	3,654 (59.06%)	22,806 (61.06%)	
End stage renal disease (receiving dialysis)	200 (2.91%)	134 (1.81%)	107 (1.73%)	759 (2.03%)	<0.01
Chronic lung disease	2,451 (35.64%)	2,854 (38.62%)	2,372 (38.34%)	13,694 (36.66%)	<0.01
Hypertension	4,353 (63.30%)	4,665 (63.13%)	3,977 (64.28%)	23,958 (64.14%)	<0.01
Hyperlipidemia	2,108 (30.65%)	2,244 (30.37%)	1,626 (26.28%)	10,999 (29.45%)	<0.01
Diabetes mellitus	1,717 (24.97%)	1,899 (25.70%)	1,445 (23.36%)	8,010 (21.45%)	<0.01
Myocardial infarction within 3 months	321 (4.67%)	346 (4.68%)	244 (3.94%)	1,457 (3.90%)	<0.01

Percutaneous coronary intervention	242 (3.52%)	267 (3.61%)	187 (3.02%)	1,250 (3.35%)	0.244
Unstable angina	1,036 (15.06%)	1,251 (16.93%)	1,050 (16.97%)	5,869 (15.71%)	<0.01
Congestive heart failure	1,377 (20.02%)	1,403 (18.99%)	1,370 (22.14%)	7,28 (19.52%)	<0.01
Atrial fibrillation	953 (13.86%)	961 (13.00%)	915 (14.79%)	6,296 (16.86%)	<0.01
Arrhythmia other than atrial fibrillation	61 (0.89%)	52 (0.70%)	70 (1.13%)	359 (0.96%)	0.064
RBC transfusion (units)	3.56 ± 2.51	3.52 ± 2.52	3.38 ± 2.35	2.96 ± 2.56	<0.01
0-1 unit	717 (10.43%)	934 (12.64%)	738 (11.93%)	8,261 (22.12%)	
2 units	1,864 (27.10%)	1,817 (24.59%)	1,801 (29.11%)	11,596 (31.05%)	
3 units	1,764 (25.65%)	1,927 (26.08%)	1,513 (24.45%)	8,107 (21.71%)	
≥4 units	2,532 (36.82%)	2,712 (36.70%)	2,135 (34.51%)	9,386 (25.13%)	
Emergency surgery	248 (3.61%)	186 (2.52%)	173 (2.80%)	568 (1.52%)	<0.01
Type of surgery					<0.01
Valve surgery	2,051 (29.82%)	1,980 (26.79%)	1,543 (24.94%)	10,434 (27.94%)	
CABG	2,967 (43.14%)	3,242 (43.87%)	2,460 (39.76%)	13,750 (36.81%)	
Re-operation[a]	859 (12.49%)	1,018 (13.78%)	1,174 (18.98%)	6,482 (17.35%)	
Combined surgery[b]	538 (7.82%)	710 (9.61%)	742 (11.99%)	5,152 (13.79%)	
Thoracic aorta surgery	462 (6.72%)	440 (5.95%)	268 (4.33%)	1,532 (4.10%)	
Surgery year					<0.01
2009-2011	2,336 (33.97%)	2,661 (36.01%)	2,229 (36.03%)	13,582 (36.36%)	
2012-2014	2,509 (36.48%)	2,670 (36.13%)	2,265 (36.61%)	13,182 (35.29%)	
2015-2016	2,032 (29.55%)	2,059 (27.86%)	1,693 (27.36%)	10,586 (28.34%)	

Data are presented as number (%) or mean ± SD

RBC, red blood cells; CABG, coronary artery bypass grafting surgery.

[a] Re-operation was determined when patients received the same type of surgery more than once during the same hospitalization period.

[b] Combined surgery was defined as two or more types of cardiac surgery performed in the same hospitalization period.

3.4 Multivariable logistic regression models for in-hospital and 1-year mortality for all cardiac surgery.

The results from the multivariable logistic regression models for in-hospital and 1-year mortality in the derivation cohort are summarized in Table 8. Identified risk factors of in-hospital and 1-year mortality included age, type of surgery, emergency surgery, annual case volume and comorbidities such as end stage renal disease receiving dialysis, which were included in the risk prediction model. Table 8 showed that in-hospital mortality in institutions with case volumes between 50 and 100 per year were associated with higher risk of in-hospital mortality compared to hospitals with volumes of more than 200 cases per year (Odd ratio [OR] 2.72, 95% confidence interval [CI] 2.36-3.13, $p < 0.01$, Table 8). For institutions with less than 50 cases per year, the independent odds ratio for in-hospital mortality was increased over threefold (OR 3.47, 95% CI 3.02-3.97, $p < 0.01$, Table 8). Similarly, institutions with case volume of 50 or less, 50-100, 100-200 had a 1.66, 2.12 and 2.79 fold increase in 1-year mortality compared to hospitals with volumes of more than 200 cases per year ($p < 0.01$ respectively, Table 8).

A total of 27 models for predicting in-hospital and 1-year mortality after cardiac surgery were devised. A model with the largest area under curve and the best calibration was selected. The inclusion of the institutional case volume to the model resulted in a statistically significant likelihood ratio difference (likelihood ratio statistic 393.12, $p < 0.001$) and the model that included case volume was selected as the final model. In addition, although transfusion was a significant risk factor for in-hospital mortality and 1-year mortality after cardiac surgery, transfusion was not included in the model in order to develop a model that will predict outcome preoperatively. Based on the model, a simple risk score system which can be used for estimating in-hospital and 1-year mortality was devised (Table 9, 10 and 11).

Table 8. Multivariable regression analysis for in-hospital mortality and 1-year mortality after cardiac surgery.

Variables	In-hospital mortality		1-year mortality	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age (years)				
18-49	Reference		Reference	
50-59	1.13 (0.89, 1.42)	0.32	1.13 (0.93, 1.36)	<0.01
60-69	1.50 (1.21, 1.86)	<0.01	1.61 (1.36, 1.92)	<0.01
70-79	2.95 (2.40, 3.63)	<0.01	3.32 (2.81, 3.92)	<0.01
≥80	5.41 (4.26, 6.87)	<0.01	6.75 (5.57, 8.18)	<0.01
Female	1.10 (0.99, 1.23)	0.08	1.05 (0.97, 1.15)	0.25
End stage renal disease (receiving dialysis)	4.90 (3.88, 6.20)	<0.01	5.13 (4.21, 6.25)	<0.01
Chronic lung disease	1.14 (1.02, 1.26)	0.02	1.17 (1.07, 1.27)	<0.01
Hypertension	1.04 (0.92, 1.18)	0.54	1.13 (1.02, 1.24)	0.02
Hyperlipidemia	1.06 (0.94, 1.19)	0.37	1.10 (1.00, 1.21)	0.05
Diabetes mellitus	1.08 (0.95, 1.23)	0.26	1.20 (1.08, 1.32)	<0.01
Myocardial infarction within 3 months	1.06 (0.81, 1.37)	0.69	1.12 (0.92, 1.37)	0.26
Percutaneous coronary intervention	1.02 (0.75, 1.39)	0.90	1.06 (0.84, 1.35)	0.63
Unstable angina	0.86 (0.72, 0.99)	0.04	0.77 (0.68, 0.88)	<0.01
Congestive heart failure	1.04 (0.91, 1.19)	0.56	1.09 (0.99, 1.22)	0.09
Atrial fibrillation	1.03 (0.89, 1.20)	0.68	1.09 (0.97, 1.23)	0.15
Arrhythmia other than atrial fibrillation	1.44 (0.89, 2.33)	0.13	1.20 (0.80, 1.81)	0.38

Emergency surgery	4.21 (3.35, 5.28)	<0.01	3.39 (2.76, 4.17)	<0.01
Type of surgery				
Valve surgery	Reference		Reference	
CABG	1.05 (0.90, 1.24)	0.54	1.11 (0.98, 1.25)	0.11
Re-operation[a]	1.98 (1.67, 2.35)	<0.01	1.78 (1.55, 2.03)	<0.01
Combined surgery[b]	2.71 (2.28, 3.20)	<0.01	2.21 (1.93, 2.53)	<0.01
Thoracic aorta surgery	3.73 (3.04, 4.58)	<0.01	3.09 (2.60, 3.67)	<0.01
Annual case volume				
≥ 200	Reference		Reference	
100 – 200	2.09 (1.78, 2.46)	<0.01	1.66 (1.45, 1.88)	<0.01
50 – 100	2.72 (2.36, 3.13)	<0.01	2.12 (1.89, 2.37)	<0.01
< 50	3.47 (3.02, 3.97)	<0.01	2.79 (2.50, 3.12)	<0.01

Data are presented as number (%) or mean ± SD

CABG, coronary artery bypass grafting surgery.

[a] Re-operation was determined when patients received the same type of surgery more than once during the same hospitalization period.

[b] Combined surgery was defined as two or more types of cardiac surgery performed in the same hospitalization period.

Table 9. Points for the prediction of in-hospital mortality and 1-year mortality

Risk factor	Categories	Point	
		In-hospital mortality	1-year mortality
Age	*18-49*	0	0
	50-59	1	1
	60-69	3	4
	70-79	9	10
	>80	14	16
Sex	*Female*	1	0
	Male	0	0
End stage renal disease (receiving dialysis)	*No*	0	0
	Yes	14	14
Chronic lung disease	*No*	0	0
	Yes	1	1
Hypertension	*No*	0	0
	Yes	0	1
Hyperlipidaemia	*Yes*	0	0
	No	0	1
Diabetes mellitus	*No*	0	0
	Yes	1	2

Myocardial infarction within 3 months	*No*	0	0
	Yes	0	1
Percutaneous coronary intervention	*No*	0	0
	Yes	0	1
Unstable angina	*Yes*	0	0
	No	1	2
Congestive heart failure	*No*	0	0
	Yes	0	1
Atrial fibrillation	*No*	0	0
	Yes	0	1
Arrhythmia other than atrial fibrillation	*No*	0	0
	Yes	3	2
Emergency surgery	*No*	0	0
	Yes	12	10
Type of surgery	*Valve surgery*	0	0
	CABG	0	1
	Re - operation	6	5
	Combined surgery	8	7
	Thoracic aorta surgery	11	10
Annual case volume	*≥200*	0	0
	100-200	6	4

50-100	9	6
<50	11	9

CABG, Coronary artery bypass grafting surgery.

Table 10. Scoring sheet

Risk factor	Categories	In-hospital mortality		1-year mortality	
		β_i	$\beta_i(W_{ij} - W_{iREF})/B$	β_i	$\beta_i(W_{ij} - W_{iREF})/B$
Age	*18-49*	0	0	0	0
	50-59	0.1175	1	0.1186	1
	60-69	0.4068	3	0.477	4
	70-79	1.0817	9	1.1988	10
	>80	1.688	14	1.9093	16
Sex	*Female*	0.0963	1	0	0
	Male	0	0	0.0512	0
End stage renal disease (receiving dialysis)	*No*	0	0	0	0
	Yes	1.59	14	1.6348	14
Chronic lung disease	*No*	0	0	0	0
	Yes	0.1265	1	0.1526	1
Hypertension	*No*	0	0	0	0
	Yes	0.0388	0	0.1186	1
Hyperlipidemia	*Yes*	0	0	0	0
	No	0.0554	0	0.0967	1
Diabetes mellitus	*No*	0	0	0	0

	Yes	0.0757	1	0.1787	2
Myocardial infarction within 3 months	*No*	0	0	0	0
	Yes	0.0536	0	0.1149	1
Percutaneous coronary intervention	*No*	0	0	0	0
	Yes	0.0196	0	0.0595	1
Unstable angina	*Yes*	0	0	0	0
	No	0.1679	1	0.2582	2
Congestive heart failure	*No*	0	0	0	0
	Yes	0.0398	0	0.0902	1
Atrial fibrillation	*No*	0	0	0	0
	Yes	0.0325	0	0.0884	1
Arrhythmia other than atrial fibrillation	*No*	0	0	0	0
	Yes	0.3671	3	0.1833	2
Emergency surgery	*No*	0	0	0	0
	Yes	1.4366	12	1.2201	10
Type of surgery	*Valve surgery*	0	0	0	0
	CABG	0.0508	0	0.1023	1
	Re - operation	0.684	6	0.5739	5
	Combined surgery	0.9949	8	0.7924	7
	Thoracic aorta surgery	1.317	11	1.1289	10
Annual case volume	*≥ 200*	0	0	0	0

	100-200	0.7386	6	0.5041	4
	50-100	0.9995	9	0.7495	6
	<50	1.2428	11	1.0256	9

CABG, Coronary artery bypass grafting surgery.

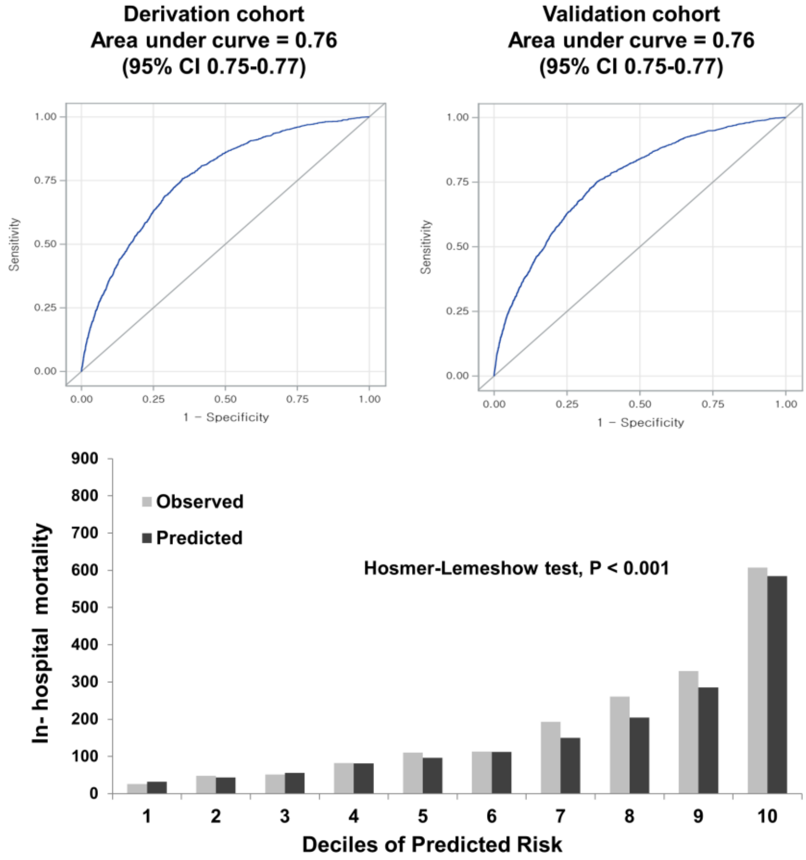
Table 11. Estimated risk of in-hospital mortality and 1-year mortality after cardiac surgery.

Points	Predicted in-hospital mortality (%)	Predicted 1-year mortality (%)
0	0.80	1.31
1	0.90	1.48
2	1.01	1.66
3	1.14	1.86
4	1.28	2.09
5	1.44	2.35
6	1.61	2.64
7	1.81	2.96
8	2.03	3.32
9	2.28	3.72
10	2.56	4.17
11	2.87	4.67
12	3.21	5.23
13	3.60	5.85
14	4.03	6.54
15	4.51	7.30
16	5.04	8.15
17	5.63	9.08
18	6.29	10.11
19	7.02	11.24
20	7.83	12.48
21	8.72	13.83
22	9.70	15.31
23	10.78	16.91
24	11.96	18.64
25	13.26	20.51
26	14.67	22.51
27	16.20	24.64
28	17.86	26.91
29	19.65	29.31
30	21.57	31.82
31	23.62	34.45
32	25.81	37.17
33	28.12	39.98
34	30.56	42.86
35	33.11	45.79
36	35.76	48.74
37	38.50	51.70
38	41.32	54.66
39	44.19	57.58
40	47.11	60.44

41	50.04	63.24
42	52.97	65.95
43	55.89	68.56
44	58.76	71.06
45	61.58	73.44
46	64.32	75.69
47	66.96	77.80
48	69.51	79.78
49	71.94	81.63
50	74.25	83.34
51	76.43	84.92
52	78.48	86.38
53	80.40	87.72
54	82.19	88.94
55	83.84	90.05
56	85.37	91.07
57	86.78	91.98
58	88.07	92.82
59	89.25	93.57
60	90.33	94.25
61	91.31	94.86
62	92.19	95.41
63	93.00	95.90
64	93.73	96.34
65	94.38	96.74
66	94.97	97.09
67	95.51	97.41
68	95.98	97.69
69	96.41	97.94

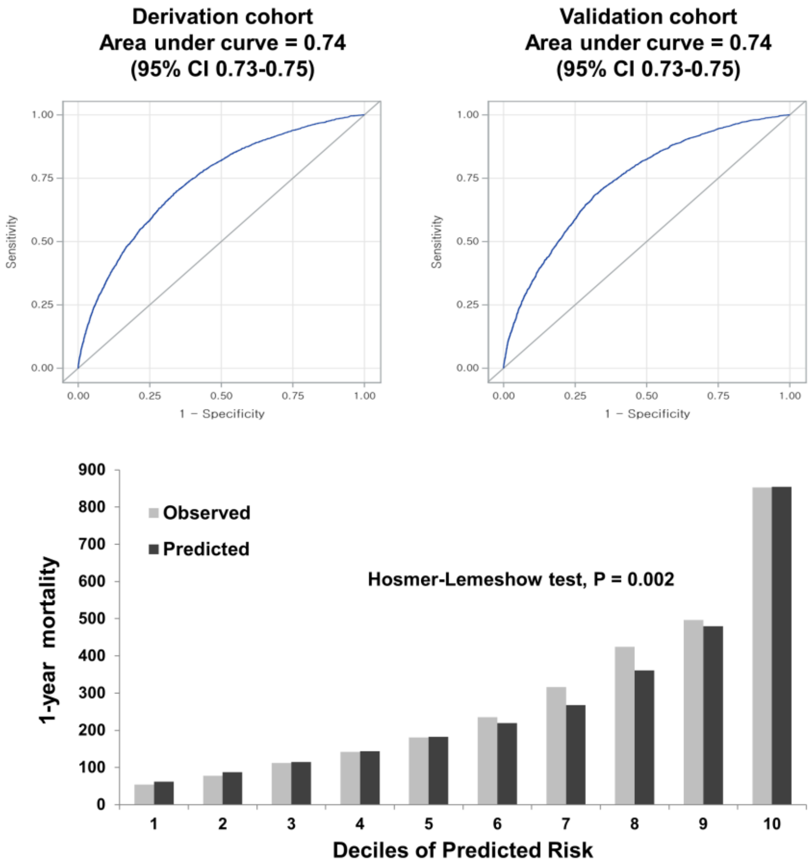
3.5 Discrimination and calibration of novel mortality prediction model.

The performance of the risk prediction models was then evaluated for each of the derivation and validation cohorts. The c-statistics for in-hospital mortality were 0.76 (95% CI, 0.75-0.77) in the derivation cohort and 0.76 (95% CI, 0.75-0.77) in the validation cohort. The c-statistics for 1 year-mortality were 0.74 (95% CI, 0.73-0.75) in the derivation cohort and 0.74 (95% CI, 0.73-0.75) in the validation cohort, indicating good discrimination. The ratio of predicted risk to observed risk of in-hospital mortality and 1 year-mortality were almost 1, indicating very good calibration (Figure 3 and Figure 4)



	1	2	3	4	5	6	7	8	9	10
Observed	0.009	0.016	0.018	0.028	0.038	0.039	0.067	0.090	0.114	0.210
Predicted	0.011	0.015	0.020	0.028	0.033	0.039	0.052	0.071	0.099	0.202
Observed/Predicted	0.816	1.115	0.909	1.007	1.140	1.005	1.289	1.278	1.154	1.039

Figure 3. Calibration for in-hospital mortality



Observed	0.019	0.027	0.039	0.049	0.063	0.081	0.110	0.147	0.172	0.295
Predicted	0.022	0.030	0.039	0.050	0.063	0.075	0.093	0.125	0.166	0.296
Observed/Predicted	0.867	0.889	0.979	0.988	0.991	1.072	1.179	1.175	1.034	0.998

Figure 4. Calibration for 1-year mortality

4. Discussion

New cardiac surgery risk models for predicting in-hospital and 1-year mortality using baseline patient characteristics, comorbidities, and hospital case volume were developed. The new model requires significantly fewer variables compared to STS or EuroSCORE, no laboratory data, and most importantly incorporates the impact of surgical experience. The STS score and EuroSCORE are risk models which were designed to predict mortality after adult cardiac surgery.[22,23] Due to advances in cardiac surgery, EuroSCORE II tends to overestimate the in-hospital mortality in low-risk patients, while underestimating in-hospital mortality in high-risk patients.[2] Accordingly, this issue raises the need for novel mortality prediction model that reflects recent advances in cardiac surgery.

The relationship between surgical case volume and patient outcome has been shown consistently across high-risk surgical procedures such as abdominal aortic aneurysm repair, esophageal resection, and heart transplantation.[10-12] Similar relationships have been shown in coronary artery bypass graft surgery[13] and valve surgery.[14,15] As this study showed above, there was a strong correlation between institutional CABG case volume and postoperative outcome. Annual CABG case volume negatively correlated with 1-year mortality as well as with in-hospital and 3- and 5-year mortality. In addition, long term survival after CABG was the highest in high volume centers where more than 50 CABGs were performed each year. In this study, case volume was still an important factor associated with better outcome after CABG, reflecting current technological advances on CABG which contribute to decrease in mortality. In addition, I showed that long term survivals were superior in high volume centers compared to the low and medium centers.

The proposed results implies that complicated surgeries require a comprehensive management, which includes not only flawless surgical skill, but also preoperative pathophysiologic evaluation, postoperative intensive care, infection prevention, and nutritional support.[24] The required comprehensive patient care are more likely to be feasible in centers with large case volume.[25] High volume centers with greater resources may be more likely to produce proficient protocols which may evolve and improve with accumulating experiences leading to better performance compared to low or medium volume centers. Specifically, high volume centers are more likely to have surgeons with accumulated experience due to the high case volume.[26,27] Comprehensive consultation systems to manage various medical and interventional complications are more readily available in high volume centers,[28] leading to a more thorough post-discharge follow up, which may have led to a better long-term mortality.

As such, although case volume has been associated with patient outcomes and reflects surgical performance, risk models developed thus far were based solely on patient characteristics and surgical factors. Furthermore, case volume may reflect not only the surgical technique, but also the institutional clinical experience in anesthesia, postoperative care, nursing, and rehabilitation. Case volume may be an important factor in predicting mortality as shown in our model, which displayed good calibration despite using a smaller number of variables. Considering that case volume was the only factor that was not used in previous models, the use of case volume as an indicator of diagnostic accuracy, operative experience, postoperative management and proficiency seems to be the discriminative factor. The higher accuracy in predicting mortality in high-risk patients compared to previous models may be explained by the fact that case volume effect is more prominent in high risk procedures.[29]

In addition to incorporating institutional case volume, our models offer risk prediction for patients undergoing reoperation and thoracic aorta surgery. Reoperation is considered an important predictive factor for mortality for cardiac surgery patients and had been incorporated in a mortality prediction models.[30] Without separate consideration for reoperation, the risk for these patients may be underestimated as reoperations would be considered equal to operations that did not require reoperation. Also, our model included thoracic aortic surgery and despite the large size of the data, was able to acquire comparable sample size for each type of cardiac surgery. This is in contrast to existing models such as the EuroSCORE in which 63.6% of patients received isolated CABG and 29.8% of patients underwent valvular operations.[31]

The STS score consists of 67 variables ranging from baseline information such as age, sex, and ethnicity to lifestyle factors such as tobacco and alcohol use. Detailed medical history including family history of premature coronary artery disease, cancer history within 5 years, mediastinal radiation, and sleep apnea are also required. EuroSCORE II, revised in 2011, consists of 17 to 26 baseline information (depending on the version) and clinical/functional status including end stage renal disease, extracardiac arteriopathy, poor mobility, and critical preoperative state. The extensive number of variables required may not be feasible in urgent situations and the accuracy of the model may be undermined in proportion to the amount of missing information. However, our new model may predict mortality accurately using relevant baseline information and institutional case volume without laboratory results.

Some limitations of the present study should be discussed. First, clinical variables associated with mortality after cardiac surgery were not included in the model. Such variables include left ventricular ejection fraction[32] and renal function,[33] which were substituted with previous diagnoses/history of angina, congestive heart failure, MI, and PCI, and with dialysis and chronic kidney disease. Due to the administrative nature of the database, the role of individual surgeons or complexity of the surgical procedure also could not be incorporated in the model. One of the main advantages of this model was that the risk can be calculated before clinical evaluation as it only uses baseline patient characteristics, comorbidities, and the case volume of the institution. Second, similar to the first limitation, baseline characteristics such as the preoperative EuroSCORE,[1] or STS score[34] were not accounted for due to limited availability of data required to calculate the scores. Postoperative outcomes are affected by the patient's pre-existing conditions, as shown in the predictive power of risk scores. Although our model lacked the information on the distribution of patients in each center, it was still able to show the significance of case volume, despite there was a higher proportion of patients with higher volume centers in various diseases. Thirds, as the model was derived and validated with Korean health insurance data, caution should be taken when applying this model to other healthcare environments. For example, although 5-year all-cause mortality of CABG was reported about 8%-10% depending on underlying comorbidities of patients,[35] the current study showed relatively higher mortality compared to these findings. It may reflect the Korean health care environment where CABGs are being performed on relatively high-risk patients, and poor performance of small volume centers resulting from centralized medical systems may have caused higher mortality compared to previous studies. In addition, as the value of the EuroSCORE and the STS were limited in ethnicities other than Caucasian,[36-40] our model will require validation in ethnicities other than Asian/Korean. However, our model suggests that it may be relevant to incorporate data at the institutional level, not just patient level data, for risk prediction after high-risk procedures such as cardiac surgery. Fourth, the impact of case volume on the model may differ in healthcare environments where cardiac surgery is not heavily concentrated to a small number of centers. As shown in our results, more than 60% of the patients received cardiac surgery in high case volume centers. In regions/countries where cardiac surgery is more evenly distributed, the impact of case volume on the model is likely to be less pronounced. Lastly, the surgeon volume was not analyzed in this study and information about the resources of each hospital or medical utilization could not be obtained. Although there is little doubt that surgical skill is a significant factor associated with patient outcome, it seems more likely that surgical skill is one of the components of the comprehensive care that is provided to the patient, from preoperative evaluation and optimization to postoperative recovery and rehabilitation.

In conclusion, higher institutional case volume of CABG was still associated with better postoperative outcomes including in-hospital mortality and mid-term mortality compared to institutions with low or medium case volume, even with advances in surgery and technology. Furthermore, considering the importance of case volume on postoperative outcome after cardiac surgery, the novel mortality prediction model incorporating case volume could be needed.

Therefore, this study showed the newly developed and validated risk prediction model for in hospital and 1-year mortality after cardiac surgery with good discrimination and calibration. The model may provide risk prediction for patients undergoing cardiac surgery using baseline characteristics, type of surgery, and hospital case volume.

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초 록

여러 연구에 따르면 기관내 수술 건수가 많을수록 관상동맥우회술 (CABG) 후 낮은 사망률을 보인다고 보고되고 있으나 대부분의 연구가 CABG의 최근에 이루어진 기술적 및 수술 발전을 반영하지 않기 때문에 수술 건수와 수술 후 결과 간의 연관성은 재평가가 필요하다. 또한 심장 수술 후 단기 사망률을 예측하는 대부분의 위험 예측 모델은 환자병력, 검사 결과 및 수술 종류 등과 같은 요인들을 포함하고 있지만 수술적 경험, 외과의의 경험 등과 같이, 수술 후 예후에 영향을 미칠 만한 요인을 포함한 모델은 부재하다. 기존 연구에서 밝혀진 바와 같이, 고위험 시술 및 수술에서 기관내 수술 건수가 시술/수술 후 예후에 미치는 영향을 고려하였을 때, 심장 수술에서 기관내 수술 건수를 요인으로 포함한 새로운 사망률 예측 모델에 대한 필요성이 제기된다. 본 연구에서는 기관내 수술 건수가 관상동맥우회술 후 임상적 결과에 미치는 영향을 알아보고, 더 나아가 기관내 수술 건수를 수술적 지표, 수술적 경험에 대한 대변도구로 판단 하, 심장 수술 후 사망률을 예측하는 모델에 하나의 요인으로서 포함하여 성능을 분석하였다.

2009년부터 2016년까지 CABG를 받은 18세 이상 성인 환자는 CABG 시술코드로 대한민국 국민건강보험 데이터베이스를 검색해 확인했다. 병원은 연간 진료규모를 기준으로 연간 20건 미만인 기관 (low volume center), 연간 20-50건 시행하는 기관 (medium volume

center) 및 연간 50건 이상 시행하는 기관 (High volume center)으로 3개 그룹으로 분류하였다. 그리고 국민건강보험데이터를 이용하여 2009년부터 2016년동안 시행된 모든 성인 심장환자들을 추출하였다. 총 57,804명에서 무작위로 유도표본 (Derivation cohort, n=28,902) 과 검증 표본 (Validation cohort, n=28,902)으로 구분하였다. 유도 표본을 이용하여 입원내 사망률과 1년 사망률에 대한 예측모델을 구현하고, 이를 검증표본을 통해 검증능력을 평가하였다. 평균 연간 심장 수술 사례를 기초로 50개 미만, 50-100개, 100-200개, 200개 이상 수술을 시행한 기관으로 구분하여 분석하였다.

관상동맥우회술 이후의 전체 1년 사망률은 연간 50건 이상 시행하는 기관(6.5%)에서 가장 낮았고, 연간 20-50건 시행하는 기관(10.6%)과 연간 20건 미만으로 시행하는 기관(15.2%)이 뒤를 이었다. 로지스틱 회귀 분석에서는 연간 20-50건 시행하는 기관(OR 1.30[95% CI 1.15-1.49], P < 0.01) 및 연간 20건 미만으로 시행하는 기관 (OR 1.75[95% CI 1.51-2.03], P < 0.01)을 연간 50건 이상 시행하는 기관과 비교하여 관상동맥우회술 이후 1년 사망률에 대한 위험 요인으로 지목하였다. 콕스 비례 위험 모델에서, 연간 20건 미만으로 시행하는 기관 및 연간 20-50건 시행하는 기관은 생존에 영향을 미치는 위험 요소였다(각각 HR 1.41 [95% CI 1.31-1.54], P < 0.01; HR 1.26 [95% CI 1.17-1.35], P < 0.01). 새롭게 구축된 모델은 병원내 사망률에서 C statistics 0.76, 1년 사망률에서 0.74 로 모델의 성능은 판별력(discrimination) 및

교정력(calibration)에서 모두 우수하였다.

관상동맥우회술을 더 많이 시행한 기관은 수술과 기술의 진보가 이루어진 현 시점에도 낮은 사망률을 보였다. 또한 심장 수술 후 수술 결과에 대한 기관의 수술건수의 중요성을 고려할 때 기관내 수술 건수를 하나의 변수로 포함하는 새로운 사망률 예측 모델이 필요성이 제기된다. 따라서, 본 연구는 검증을 거친 심장 수술 후 병원 내 및 1년 사망률에 대한 예측 모델을 새롭게 개발하고 보여주었다. 이 모델은 환자의 기본정보와 과거력, 기관내 수술 건수를 이용하여 구축된 새로운 모델로서 기존의 대표적인 모델인 STS score 와 EurosSCORE 모델에 비해 평가 변수가 적으며, 검사결과가 필요하지 않아 간편하다는 장점을 지닌다. 또한 고위험환자에서도 비교적 정확도 높은 사망률을 예측하는 것으로 평가되며, 입원내 사망률 뿐 아니라 1년이내 사망률을 예측할 수 있어 임상에서 손쉽게 이용이 가능하다.

주요어 : 심장수술, 사망률, 예측모형, 기관사례수
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