Retrospective Cohort Study

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Risk stratification model integrating nutritional and inflammatory factors for predicting 1-year mortality after valvular heart surgery: a retrospective cohort study

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Introduction: Existing risk-scoring systems for cardiac surgery include only standard preoperative factors without considering nutritional and inflammatory status or intraoperative factors. The objective of this study was to develop a comprehensive prediction model for mortality incorporating nutritional, inflammatory, and perioperative factors in patients undergoing valvular heart surgery.

Materials and methods: In this retrospective review of 2046 patients who underwent valvular heart surgery, Cox and LASSO regression analyses were performed to identify independent prognostic factors for 1-year postoperative mortality among various perioperative factors known to affect prognosis, including objective nutritional and inflammatory indices. A novel nomogram model incorporating selected prognostic factors was developed, and its discrimination ability was evaluated using the C-index. The model was validated in internal and external cohorts.

Results: The 1-year mortality rate after valvular heart surgery was 5.1% (105 of 2046 patients) and was significantly associated with several preoperative objective inflammatory and nutritional indices. Cox and LASSO analyses identified the following five independent prognostic factors for mortality: monocyte-to-lymphocyte ratio (an objective inflammatory index), EuroSCORE II, Controlling Nutritional Status score, cardiopulmonary bypass time, and number of erythrocyte units transfused intraoperatively. The nomogram model incorporating these five factors had a C-index of 0.834 (95% CI: 0.791–0.877), which was higher than that of EuroSCORE II alone (0.744, 95% CI: 0.697–0.791) ($P < 0.001$). The nomogram achieved good discrimination ability, with C-indices of 0.836 (95% CI: 0.790–0.878) and 0.727 (95% CI: 0.651–0.803) in the internal and external validation cohorts, respectively, and showed well-fitted calibration curves.

Conclusions: A nomogram model incorporating five inflammatory, nutritional, and perioperative factors, as well as EuroSCORE II, was a better predictor of 1-year mortality after valvular heart surgery than EuroSCORE II alone, with good discrimination and calibration power for predicting mortality in both internal and external validation cohorts.

Keywords: Inflammation, monocyte-to-lymphocyte ratio, mortality, nomogram, nutrition, valvular heart surgery

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HIGHLIGHTS

- Accurate risk stratification is essential for patient management, but models specific to valve heart surgery (VHS) are lacking.
- We identified several independent prognostic factors for 1-year mortality after VHS and constructed a nomogram.
- The nomogram model incorporating five simple clinical variables had excellent prediction ability and was verified in the internal and external cohorts.
- The monocyte-to-lymphocyte ratio was the most reliable predictor for mortality after VHS among objective inflammatory indices.

Introduction

Accurate risk stratification has been emphasized as essential for patient management in cardiac surgery, as it allows clinicians to plan appropriate therapeutic measures and thereby improve patient outcomes. Although valvular heart surgery (VHS) is generally associated with a worse prognosis and higher mortality

than coronary artery bypass graft surgery (CABG), the most commonly used risk-scoring system – the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) system – includes both VHS and CABG patients and was initially developed from a study population containing a higher proportion of CABG patients[1]. Of note, representative risk-scoring systems for cardiac surgery like EuroSCORE II and the Society of Thoracic Surgeons score use in-hospital mortality as a primary endpoint and consider only preoperative risk factors[1,2]. Although in-hospital mortality and 30-day mortality are important markers for early surgical complications, the period of increased mortality varies depending on the type of surgery. Notably, survival curves after VHS demonstrate a steep initial decline, followed by stabilization after 90–120 days[3]. Thus, there is an unmet need for a risk stratification model specific to VHS that predicts mortality rates beyond the time of hospitalization.

To enhance the model's performance, integration of objective nutritional and inflammatory indices that are easily calculated using routine laboratory test results and surgery-related factors merits consideration as they have been shown to exert substantial influence on prognosis[4–6]. Among the various nutritional indices, the Controlling Nutritional Status (CONUT) score, based on serum albumin, serum total cholesterol, and total lymphocyte count, was reported as the objective nutritional index most closely associated with 1-year mortality after VHS[4]. However, the inflammatory index best associated with 1-year mortality after VHS has not been investigated, while there are several candidates using ratios between neutrophil, lymphocyte, and monocyte counts that showed usefulness in patients with cardiovascular disease[5,7].

In this retrospective study, we aimed to establish a comprehensive model to predict the risk of 1-year mortality in patients undergoing VHS by first identifying the inflammatory index most closely associated with 1-year mortality and then developing a prognostic nomogram model incorporating perioperative risk factors with nutritional and inflammatory indices.

Materials and methods

Study population

Patients who underwent VHS using cardiopulmonary bypass (CPB) between January 2016 and December 2020 were retrospectively screened. Patients who required concomitant CABG surgery, aortic procedures, or other cardiac procedures in addition to VHS were also included. Patients undergoing emergency surgery were included. The exclusion criteria were as follows: 1) age below 18 years; 2) transcatheter valve replacement, combined congenital heart surgery, or implantation of a ventricular assist device; 3) lack of data required to calculate inflammatory indices; or 4) loss of follow-up. The study was approved by the Institutional Review Board and Hospital Research Ethics Committee (#4-2022-1117) and was registered at clinicaltrials.gov. The requirement for obtaining patient informed consent was waived because of the study's retrospective nature. This study has been reported in line with the STROCSS (strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery) criteria[8]. Supplemental Digital Content 1, http://links.lww.com/JS9/B155.

Data collection and outcomes assessment

Patient data were retrieved from the electronic database and included patient demographics, comorbidities, and medications. Preoperative laboratory tests (routinely collected within 1 month before surgery) included the white blood cell count with differential, hemoglobin, hematocrit, platelet count, total cholesterol, fasting glucose, albumin, creatinine, estimated glomerular filtration rate, and C-reactive protein. Intraoperative data included the type of surgery, emergency versus elective surgery, the durations of CPB and aortic cross-clamp, and the number of packed erythrocytes units transfused. Postoperative data included 1-year mortality and postoperative complications, including acute kidney injury (defined as a 0.3 mg/dl increase in serum creatinine within 48 h or need for renal replacement therapy)[9], prolonged mechanical ventilation (> 48 h), reoperation because of bleeding, and lengths of stay in the ICU and hospital. Mortality at follow-up was analyzed using time-to-event analysis, with survival time defined as the time from the date of surgery until the date of death.

Preoperative nutritional status, represented by the CONUT score, was calculated according to the CONUT scoring system using serum albumin, total cholesterol, and total lymphocyte count[10]. EuroSCORE II was calculated using the calculator provided on the EuroSCORE II website (http://www.EuroSCORE II.org). Preoperative inflammatory status was evaluated by determining the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR). NLR was calculated as the neutrophil count divided by lymphocyte count, MLR as the monocyte count divided by lymphocyte count, and PLR as the platelet count divided by lymphocyte count[5]. We also calculated the systemic immune inflammation index (SII), defined as (platelet count × neutrophil count)/lymphocyte count, and the systemic inflammation response index (SIRI), defined as (neutrophil count × monocyte count)/lymphocyte count[7,11].

Study endpoints

The primary endpoint was 1-year mortality after VHS. We developed a nomogram model for predicting 1-year mortality post-VHS by first determining the objective inflammatory index most reliably associated with mortality and then selecting preoperative variables (including the CONUT score and the inflammatory index) and intraoperative variables to incorporate into the nomogram. The predictive discrimination ability of the nomogram was evaluated and compared with EuroSCORE II alone. The nomogram model was verified in internal and external validation cohorts.

Statistical analysis

Continuous variables were not normally distributed according to the Kolmogorov–Smirnov test and were therefore analyzed using the Mann–Whitney *U*-test and presented as median (interquartile range). Categorical variables were compared using the χ^2-test or Fisher's exact test and presented as absolute numbers (percentage).

For model development, LASSO and Cox logistic regression analyses were performed to screen risk factors for mortality. Univariable Cox analysis was used to identify possible predictive factors among perioperative variables, including inflammatory and nutritional indices. LASSO regression analysis was then

performed for data dimensionality reduction and variable selection, improving prediction accuracy and interpretation. Variables with a *P* valve less than 0.05 on univariable Cox logistic regression analysis were selected for LASSO analysis. An L1 penalty was used in the LASSO model to reduce some regression coefficients to 0, and 10-fold cross-validation with λ_{1se} was performed to find the optimal log (λ). A multivariable Cox analysis was performed to identify independent predictive factors for mortality using backward stepwise selection. Variables that had a *P* value less than 0.05 in the univariable analysis were included in the multivariable analysis. Each inflammatory index was included in the model as a continuous variable, and five different multivariable models were created by including only one inflammatory index at a time. The hazard ratio with the corresponding 95% CI was calculated for each variable.

Subsequently, a prognostic model based on the selected variables was established and graphically represented as a nomogram using the "rms" package of R software. Each subclass of the selected variables was scored according to a point scale, and a total score was obtained by summing the scores for each variable. Mortality probabilities were predicted by locating the total score on the survival probability scale. The discrimination abilities and predictive performances of the nomogram model were assessed using Harrell's concordance statistic (i.e. C-index)[12], which estimates the probability of concordance between predicted and observed responses. The C-index is similar to the area under the receiver operating characteristics curve for binary outcomes: a value of 0.50 indicates no predictive discrimination, whereas a value of 1.0 indicates a perfect separation between patients with and without the event. The nomogram and EuroSCORE II were compared by calculating the C-index with bootstrapping methods. The corresponding integrated discrimination improvement and net reclassification improvement were calculated[13].

Nomogram performance was assessed through both internal and external validation processes. To decrease overfit bias and increase precision during internal validation, the nomogram model was subjected to bootstrapping validation (1000 bootstrap resamples) to evaluate a relatively corrected C-index. For external validation, the nomogram model was applied in an external validation cohort, which consisted of an independent cohort of 655 patients undergoing VHS between January 2016 and December 2020 at another tertiary hospital. The nomogram model was used to predict postoperative 1-year mortality in the external validation cohort. The discriminative ability of the model in the validation cohort was measured using the C-index, and a calibration curve was plotted to assess the calibration of the nomogram.

P value less than 0.05 were considered statistically significant for all analyses. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, New York, USA) and R package version 4.2.1 (http://www.R-project.org).

Results

From the initial group of 2066 patients, we excluded eight patients who underwent combined congenital heart surgery and 12 patients lacking the data necessary for calculating the inflammatory indices. The remaining 2046 patients with complete preoperative inflammation data and postoperative follow-up data were included in the analysis (Fig. 1).

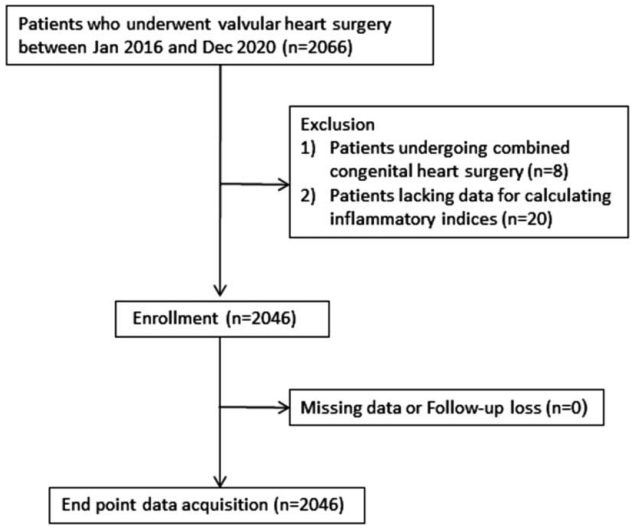


Figure 1. Consort diagram.

Baseline characteristics

The 1-year mortality rate was 5.1% (105 of 2046 patients). The demographics, clinical data, and laboratory findings of the deceased and nondeceased patients are shown in Tables 1 and 2. Deceased patients had a higher age, lower BMI, higher EuroSCORE II, and lower left ventricular ejection fraction than nondeceased patients. The deceased group also had a higher prevalence of diabetes, chronic kidney disease, recent myocardial infarction, cerebrovascular disease, chronic lung disease, congestive heart failure, preoperative use of a renin–angiotensin system inhibitor, longer CPB time, and a higher number of intraoperative erythrocytes units (Table 1).

All inflammatory indices, including NLR, MLR, PLR, SII, and SIRI, were significantly higher in deceased patients than in nondeceased patients. The CONUT score was higher, and the hemoglobin concentration and platelet count were significantly lower in the deceased group. Deceased patients also had significantly lower serum cholesterol, albumin, and estimated glomerular filtration rate and higher creatinine and C-reactive protein than the nondeceased patients (Table 2).

Prognostic factors identification

In univariable Cox regression analysis to determine possible predictors of mortality, all inflammatory indices were significantly associated with mortality ($P < 0.05$). Among the inflammatory indices, MLR had the highest C-index for predicting 1-year mortality (0.768, 95% CI: 0.720–0.817) (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/B156). In multivariable Cox regression analysis, EuroSCORE II, CONUT score, MLR, CPB time, and the number of intraoperative erythrocytes units were significantly associated with 1-year mortality after VHS (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/B156). When the selected variables were continuous values, the predictive discrimination power (C-index) of the multivariable Cox regression model was 0.832 (95% CI: 0.788–0.875).

Table 1

Demographic and clinical data.

	All ($n=2046$)	Nondeceased ($n=1941$, 94.9%)	Deceased ($n=105$, 5.1%)	*P*
Age (years)	66 (57, 73)	65 (56, 73)	73 (65, 78)	< 0.001
Male	1006 (49.2)	942 (48.5)	64 (61.0)	0.013
BMI (kg/m^2)	23.4 (21.2, 25.8)	23.5 (21.3, 25.8)	22.3 (19.8, 24.9)	0.001
Morbidity				
Hypertension	1047 (51.2)	983 (50.6)	64 (61.0)	0.040
Diabetes mellitus	416 (20.3)	383 (19.7)	33 (31.4)	0.004
Chronic kidney disease	232 (11.3)	188 (9.7)	44 (41.9)	< 0.001
MI within 3 months	56 (2.7)	45 (2.3)	11 (10.5)	< 0.001
Cerebral vascular disease	298 (14.6)	273 (14.1)	25 (23.8)	0.006
Chronic lung disease	73 (3.6)	64 (3.3)	9 (8.6)	0.005
Congestive heart failure	377 (18.4)	341 (17.6)	36 (34.3)	< 0.001
EuroSCORE II	4.0 (1.5, 6.4)	3.7 (1.4, 6.0)	8.0 (4.8, 10.8)	< 0.001
LVEF (%)	64 (57, 70)	64 (57, 70)	57 (44, 66)	< 0.001
Medication				
Beta-blocker	712 (34.8)	677 (34.9)	35 (33.3)	0.746
CCB	509 (24.9)	482 (24.8)	27 (25.7)	0.839
RASi	1073 (52.4)	1030 (53.1)	43 (41.0)	0.015
Statin	870 (42.5)	816 (42.0)	54 (51.4)	0.058
Diuretics	1369 (66.9)	1295 (66.7)	74 (70.5)	0.425
Type of surgery				
Aortic valve surgery	642 (31.4)	617 (31.8)	25 (23.8)	< 0.001
Mitral valve surgery	742 (36.3)	714(36.8)	28 (26.7)	
Double valve surgery	293 (14.3)	272 (14.0)	21 (20.0)	
Valve + CABG	147 (7.2)	126 (6.5)	21 (20.0)	
Valve + aorta surgery	124 (6.1)	122 (6.3)	2 (1.9)	
Tricuspid valve surgery	98 (4.8)	90 (4.6)	8 (7.6)	
Emergency operation	38 (1.9)	30 (1.5)	8 (10.3)	< 0.001
CPB time (min)	99 (72, 130)	98 (71, 128)	129 (86, 169)	< 0.001
ACC time (min)	65 (44, 87)	65 (44, 87)	72 (45, 109)	0.098
Intraoperative erythrocyte transfusion (unit)	0 (0, 1)	0 (0, 1)	2 (1, 3)	< 0.001

Values are median (IQR) or number (percentage).

ACC, aortic cross-clamp; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CPB, cardiopulmonary bypass; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RASi, renin–angiotensin system inhibitor.

Table 2

Preoperative laboratory findings and inflammatory and nutritional indices.

	All ($n=2046$)	Nondeceased ($n=1941$, 94.9%)	Deceased ($n=105$, 5.1%)	*P*
NLR	2.08 (1.47, 3.04)	2.04 (1.46, 2.91)	3.93 (2.44, 7.14)	< 0.001
PLR	117.5 (88.8, 155.0)	116.7 (88.4, 152.7)	141.4 (96.0, 229.3)	< 0.001
MLR	0.22 (0.17, 0.31)	0.22 (0.17, 0.30)	0.43 (0.25, 0.69)	< 0.001
SIRI	0.75 (0.49, 1.23)	0.73 (0.48, 1.15)	1.55 (0.90, 3.87)	< 0.001
SII	391.3 (265.8, 598.7)	386.5 (263.6, 586.4)	573.8 (344.6, 1233.7)	< 0.001
CONUT score	2 (1, 3)	2 (1, 3)	5 (2, 7)	< 0.001
Hemoglobin (g/dl)	12.5 (11.0, 13.8)	12.6 (11.2, 13.8)	10.1 (9.1, 11.9)	< 0.001
Platelet ($10^3/\mu l$)	189 (153, 233)	191 (156, 235)	149 (112, 210)	< 0.001
White blood cell (/mm^3)	5810 (4746, 7150)	5804 (4742, 7098)	6280 (4785, 8625)	0.055
Neutrophil (/mm^3)	3350 (2590, 4432)	3310 (2580, 4365)	4190 (2755, 6420)	< 0.001
Lymphocyte (/mm^3)	1645 (1190, 2090)	1670 (1230, 2110)	1050 (690, 1475)	< 0.001
Monocyte (/mm^3)	370 (290, 460)	360 (290, 460)	410 (300, 555)	0.004
Total cholesterol (mg/dl)	156 (132, 186)	158 (133, 187)	133 (116, 152)	< 0.001
Glucose (mg/dl)	107 (95, 130)	107 (95, 129)	110 (95, 147)	0.458
Albumin (g/dl)	4.0 (3.7, 4.3)	4.1 (3.7, 4.3)	3.4 (2.9, 3.9)	< 0.001
Creatinine (mg/dl)	0.82 (0.68, 0.99)	0.82 (0.68, 0.98)	1.17 (0.85, 1.95)	< 0.001
eGFR (ml/min/1.73m^2)	83.0 (66.0, 95.0)	84.0 (67.5, 96.0)	54.1 (27.1, 79.8)	< 0.001
C-reactive protein (mg/l)	2.2 (0.7, 9.1)	1.9 (0.7, 7.2)	13.1 (2.7, 44.7)	< 0.001

Values are median (IQR).

CONUT score, Controlling Nutritional Status score; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SIRI, systemic inflammatory response index.

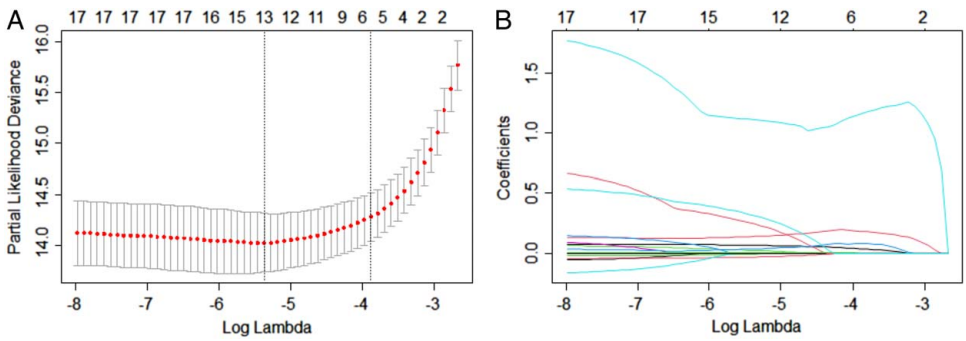


Figure 2. Variable selection using the LASSO logistic regression model. (A) Ten-fold cross-validation for tuning parameter selection in the LASSO model. (B) LASSO coefficient profiles.

Variables with *P* value less than 0.05 in univariable Cox analysis were included in LASSO regression analysis for dimensionality reduction and variable selection. To prevent multicollinearity, we excluded variables that were also included in EuroSCORE II: age, sex, diabetes, chronic kidney disease, chronic lung disease, recent myocardial infarction, congestive heart failure, left ventricular ejection fraction, operation type, and emergency surgery. The LASSO coefficient profiles of the variables were plotted as partial likelihood deviance versus log (λ) (Fig. 2A). We chose the optimum value of λ corresponding to 1 SE of the minimum criteria. Optimum parameter (λ) selection in the LASSO model was performed using 10-fold cross-validation (Fig. 2B). Five variables, including EuroSCORE II, CONUT score, MLR, CPB time, and number of intraoperative erythrocytes units, were selected with nonzero coefficients at an optimal log (λ) value of – 3.89. These five variables were the same as those found to be independent predictors of 1-year mortality in multivariable Cox analysis. The variance inflation factor was calculated and revealed no multicollinearity in the model. MLR was the only inflammatory index selected in both the LASSO and Cox analyses (Table 3 and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/B156).

Nomogram model development

A prognostic nomogram model for predicting mortality was developed by incorporating the five prognostic factors derived from the LASSO and Cox analyses. The values of MLR, EuroSCORE II, CPB time, CONUT score, and number of intraoperative erythrocyte units were 0.05–3.11, 0.50–47.78, 33–515, 0–12, and 0–13, respectively. For scores of variables with wide ranges (MLR, EuroSCORE II, and CPB time), a categorical scoring system was used to simplify the nomogram and facilitate data entry into the model. We used the Contal and O'Quigley methods to determine the cutoff value of MLR with the best predictive value for 1-year mortality; this cutoff value was 0.32. The cutoff values for EuroSCORE II (8%) and CPB time (120 min) were based on guidelines and clinical relevance[14]. The CONUT score and units of intraoperative erythrocytes were kept as continuous values. Each prognostic factor was assigned weighted scores in the nomogram. By summing the score of each prognostic factor subclass, a total score was obtained for each patient, and the probability of 1-year mortality was predicted by locating the total score on the probability of 1-year mortality scale (Fig. 3).

Table 3

Multivariable Cox analysis of prognostic factors for mortality after valvular heart surgery.

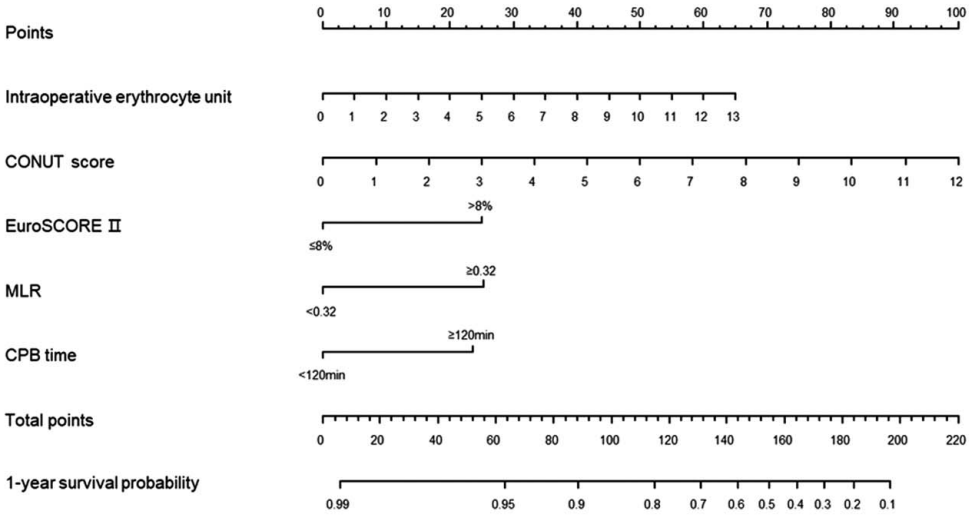
Variables	Hazard ratio	95% CI	*P*
EuroSCORE II			
≤ 8%	ref		
> 8%	2.038	1.283–3.237	0.003
Controlling Nutritional Status score[a]	1.269	1.164–1.383	< 0.001
Monocyte-to-lymphocyte ratio			
< 0.32	ref		
≥ 0.32	2.057	1.264–3.348	0.004
Cardiopulmonary bypass time			
< 120 min	ref		
≥ 120 min	1.965	1.270–3.040	0.002
Intraoperative erythrocyte transfusion[a]	1.154	1.045–1.275	0.005

[a]For each 1-unit increment.

Nomogram model validation

Predicted discrimination (C-index) of the nomogram model was 0.834 (95% CI: 0.791–0.877), which was significantly higher than that of EuroSCORE II (0.744, 95% CI: 0.697–0.791, $P < 0.001$) alone. Integration of five prognostic factors into the nomogram resulted in significant improvement in the predictive value for 1-year mortality, as evaluated using the net reclassification improvement and integrated discrimination improvement (all $P < 0.001$) (Table 4).

The discrimination and calibration of the nomogram for predicting 1-year mortality were evaluated in both internal and external validation cohorts. Calibration curves were constructed to demonstrate the optimal agreement for the probability of survival between nomogram predictions and actual observations. In the internal validation cohort, the C-index of the nomogram was 0.836 (95% CI: 0.790–0.878) through bootstrapping validation, and the calibration curve with bootstrapping also showed good calibration (Fig. 4A). For external validation, the nomogram model was applied in an independent cohort in another tertiary hospital, with different demographics, clinical data, and laboratory findings compared to the primary cohort (Supplemental Table 2, Supplemental Digital Content 3, http://links.lww.com/JS9/B157). The 1-year mortality rate was higher in the external validation cohort compared to the primary cohort [7.8% (51 of 655 patients) vs. 5.1% (105 of 2046 patients),



Intraoperative erythrocyte unit	Points	CONUT score	Points	EuroSCORE II	Points	Total points	1-year survival probability
0	0	0	0	≤8%	0	196	0.10
1	5	1	8	>8%	25	184	0.20
2	10	2	17			174	0.30
3	15	3	25	**MLR**	**Points**	164	0.40
4	20	4	33	<0.32	0	154	0.50
5	25	5	42	≥0.32	25	144	0.60
6	30	6	50	**CPB time**	**Points**	131	0.70
7	35	7	58	<120min	0	115	0.80
8	40	8	67	≥120min	24	88	0.90
9	45	9	75			63	0.95
10	50	10	83			6	0.99
11	55	11	92				
12	60	12	100				
13	65						

Figure 3. Nomogram model for predicting 1-year mortality after valvular heart surgery. CPB, cardiopulmonary bypass; MLR, monocyte-to-lymphocyte ratio.

$P = 0.011$]. In the external validation cohort, the C-index of the nomogram was 0.727 (95% CI: 0.651–0.803), which was higher than that of the EuroSCORE II alone (0.635, 95% CI: 0.555–0.715, $P = 0.029$). The nomogram significantly improved the predictive value for 1-year mortality, as evaluated using the net reclassification improvement (0.296, 95% CI: 0.121–0.422, $P < 0.001$). The external validation cohort also showed well-fitted calibration curves (Fig. 4B).

Table 4

Comparison of EuroSCORE II and nomogram.

	EuroSCORE II	Nomogram	*P*
C-index (95% CI)	0.744 (0.697–0.791)	0.834 (0.791–0.877)	< 0.001
Net reclassification improvement (95% CI)	ref	0.445 (0.337–0.541)	< 0.001
Integrated discrimination improvement (95% CI)	ref	0.097 (0.053–0.163)	< 0.001

Values are median (IQR) or number (percentage).
IQR, interquartile range.

Discussion

Main finding

In this retrospective study, we developed a predictive nomogram model for 1-year mortality after VHS incorporating five perioperative prognostic factors: EuroSCORE II, CONUT score, MLR, CPB time, and the number of erythrocytes units transfused intraoperatively. Of these factors, MLR had the highest predictive value for mortality among the inflammatory indices, indicating MLR as the most reliable inflammatory index predictor for 1-year mortality after VHS. The nomogram model had excellent prediction ability, with a C-index of 0.834 (which was superior to that of EuroSCORE II alone) and good discrimination and calibration power in predicting 1-year mortality in both internal and external validation cohorts.

Nutritional and Inflammatory indices

Patients with cardiovascular diseases have an increased risk of malnutrition because of insufficient caloric intake and increased

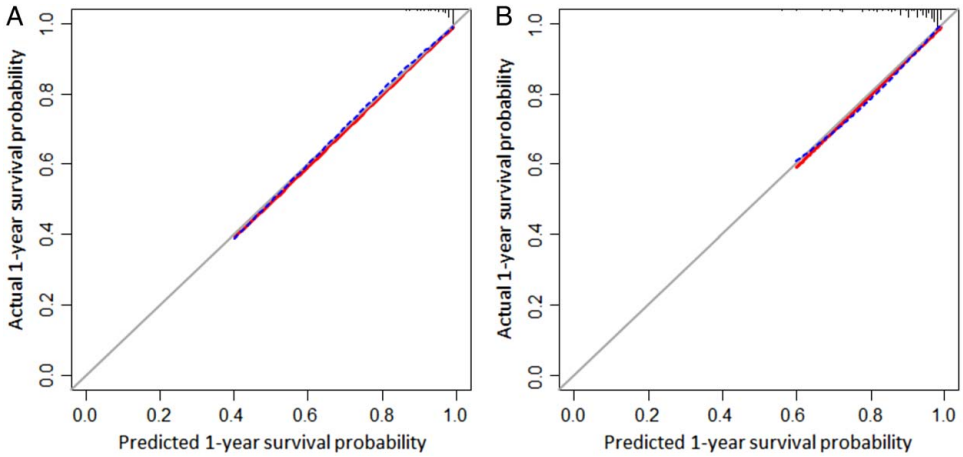


Figure 4. Calibration plot in the internal (A) and external validation cohorts (B) ideal (gray solid line); observed (red solid line); optimism corrected (blue dotted line).

catabolism[15]. Inflammation also plays a critical role in the pathogenesis of cardiovascular disorders[16]. Indeed, malnutrition and inflammation have been associated with the severity and rate of progression of valvular heart disease[17–19]. However, there are limited published studies on risk stratification considering both nutrition and inflammation in patients undergoing VHS. The CONUT score was reported to be an objective nutritional index closely associated with 1-year mortality in patients after VHS[4]. However, no study has heretofore evaluated the prognostic ability of objective inflammatory indices to predict patient outcomes after VHS, despite these patients having a high risk of CPB-induced inflammation.

The prognostic values for mortality and morbidity of objective inflammatory indices composed of white blood cell subtype and platelet counts have been determined for cardiovascular interventions[20,21] and surgery[5,22,23]. Combining inflammatory markers in objective inflammatory indices improves predictive accuracy, compared with individual markers, by accounting for complex nonlinear relationships between proinflammatory and anti-inflammatory responses. Most inflammatory indices use a combination of neutrophils, platelets, monocytes, and lymphocytes, which are well-known key mediators of inflammatory reactions. A recent study reported that a high preoperative NLR (the most widely investigated inflammatory index) was independently associated with increased mortality after aortic valve replacement[24]. That study, however, was a case mix of patients undergoing surgery and transcatheter procedures and investigated only NLR, not other inflammatory indices.

In the current study, we evaluated various inflammatory indices, including NLR, MLR, PLR, SII, and SIRI, and found that all inflammatory indices were significantly associated with 1-year mortality. Further, MLR was the most relevant inflammatory index for predicting 1-year mortality in patients undergoing VHS, with the highest C-index among all inflammatory indices. Notably, previous studies comparing the predictive ability of inflammatory indices combined candidate inflammatory parameters with strong collinearity and correlation and entered them into multivariable Cox models to identify independent predictors; this can lead to conflicts between parameters as well as statistical problems[5,20]. In contrast, we performed LASSO analysis to select the most important inflammatory index while avoiding the effects of multicollinearity between indices. Only MLR was chosen as an independent predictor of mortality, even after adjusting for other perioperative factors.

Nomogram model development

Nomograms are a reliable tool to integrate and quantify potential risk factors by assigning a score to each factor[25], and they have been actively studied in the field of cancer management[26–29]. In CABG patients with heart failure, a nomogram model for predicting in-hospital mortality had a better C-index than EuroSCORE II alone, highlighting the usefulness of a risk stratification nomogram tailored to the characteristics of the surgical patient group[30,31]. Several studies previously verified variables other than EuroSCORE II as being closely related to overall patient outcomes and postoperative mortality after cardiac surgery[4,22,32,33], but these were not included in previous risk-scoring systems. Consistent with the results of a previous study[4], our findings reconfirmed that preoperative nutritional status, as assessed by the CONUT score, was significantly associated with mortality after VHS. In addition, we confirmed the association between preoperative inflammation and mortality and first demonstrated that MLR was the most reliable inflammatory index predictor in 1-year mortality after VHS. The nomogram model incorporating selected five variables (confirmed to have no multicollinearity) showed favorable discrimination, with a C-index greater than 0.8 and good calibration in the primary and internal validation cohorts. In contrast, EuroSCORE II alone had a lower C-index compared to the nomogram and underestimated mortality, supporting the benefit of integrating new perioperative variables in our model.

Apart from long-term mortality, 1-year mortality risk should be assessed to fully appreciate the peaking mortality rate beyond 30 days or the index hospitalization in clinical practice, which may provide clinicians with essential information for creating individualized treatment strategies after VHS. The nomogram model developed in this study is a simple, reliable, and reproducible scoring system based on only five variables and has the advantages of convenience, high accuracy, and efficiency. It can be applied in clinical practice to provide valuable information for postoperative management strategies to improve the long-term prognosis after VHS at increased risk of mortality.

Limitations

There are limitations to this study. First, it is based on single-center retrospective data despite external validation, and the nomogram model was developed in a very small cohort of only 105 patients who experienced the outcome (i.e. death within 1 year after VHS). However, there was almost no missing data for evaluating the primary endpoint, and we validated the nomogram through both internal and external validation and found good discrimination and calibration in both cohorts. Despite the internal and external validation, the nomogram model was verified only with another small cohort in the same country, and thus further validation in a larger and more diverse group of patients is warranted for generalization. Second, this study included all types of VHS, as well as VHS combined with CABG or aortic surgery. However, this may also be considered an advantage, as it makes our results applicable to all patients undergoing VHS.

Conclusion

In conclusion, EuroSCORE II, CONUT score, MLR, CPB time, and number of intraoperative erythrocytes units were independent prognostic factors for 1-year mortality after VHS. Our nomogram model incorporating these simple clinical variables showed better predictive accuracy for mortality than EuroSCORE II alone, suggesting that it can be a useful, practical tool to identify patients at high risk of mortality. In addition, our results confirmed the association between preoperative inflammation and increased mortality after VHS, revealing that MLR was the most reliable objective inflammatory index for predicting mortality.

Ethical approval

The study was approved by the Institutional Review Board and Hospital Research Ethics Committee of the Severance Hospital at Yonsei University College of Medicine (#4-2022-1117).

Consent

The requirement for obtaining patient informed consent was waived because of the study's retrospective nature.

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None.

Author contribution

J.S.C and Y.L.K.: study concept and design. J.S.C, Y.J.C, S.L., and H.W.C.: data collection and analysis. J.S.C, Y.J.C, J.K.S, Y.J., and Y.L.K. :interpretation of data. J.S.C. and Y.L.K.: writing original draft. J.K.S. and Y.L.K.: revising of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

Registration of clinical trials

clinicaltrial.gov (NCT05833256).

Guarantor

Young-Lan Kwak.

Data statement

The data sets used and/or analyzed for the present study are available from the corresponding author on reasonable request.

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Presentation

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