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Association between preoperative fibrinogen to albumin ratio and all-cause mortality after off-pump coronary artery bypass grafting: A retrospective observational study

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미치는 영향: 후향적 관찰연구

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박 서 영

Association between preoperative fibrinogen to albumin ratio and all-cause mortality after off-pump coronary artery bypass grafting: A retrospective observational study

지도 교수 김 태 경

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위 원 장 황 호 영 (인)

부위원장 김 태 경 (인)

위 원 김 원 호 (인)

Abstract

Background: Fibrinogen to albumin ratio (FAR) is a recently introduced prognostic marker for patient with coronary artery disease. Present study investigated whether fibrinogen to albumin ratio (FAR) is associated clinical outcome after off-pump coronary artery bypass grafting (OPCAB).

Method: We retrospectively reviewed a total of 1759 patients who underwent OPCAB. To evaluate the association between FAR and mortality in OPCAB patients, patients were divided into 4 groups based on FAR quartile. Cox proportional hazards regression analysis was used to assess the association between FAR and all-cause mortality. Propensity score matching was also conducted to compare the cumulative survival rate between higher FAR group and lower FAR group.

Results: On multivariable Cox regression analysis, preoperative FAR was an independent risk factor for all-cause mortality after OPCAB (highest quartile HR, 1.933; 95% CI, 1.129-3.310; p=0.016). After propensity score matching, the all-cause mortality was significantly higher in patients in the fourth quartile of FAR compared with those in the remaining quartiles (p=0.03).

Conclusion: Higher FAR was associated with increased all-cause mortality after OPCAB. Preoperative FAR could be a prognostic factor for predicting higher mortality after OPCAB.

Keywords: Fibrinogen to albumin ratio; Fibrinogen; Albumin; Off-pump coronary artery bypass grafting

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Introduction

Coronary artery bypass grafting (CABG) is one of the most commonly performed cardiac surgical procedure worldwide.[1,2] Morbidity and mortality after CABG decreased over the past decade, yet perioperative risk is still high.[3-5] Therefore, predicting risk and outcome of patients undergoing CABG has been a major issue. Several risk prediction models, such as European System for Cardiac Operative Risk Evaluation (EuroSCORE), Society for Thoracic Surgeons 2008 Cardiac Surgery Risk Models (STS score), have been used in cardiac surgery for decades. However, since laboratory data has not been applied to these risk prediction models, there has been a need for defining novel prognostic model that applies inflammatory data for improved patient risk stratification.

Serum fibrinogen is considered as a marker of inflammation in coronary artery disease.[6-8] Serum fibrinogen level rise not only in acute diseases such as bacterial infections, trauma, or post-surgery, but also in chronic low-grade inflammation.[9-11] Increase in serum fibrinogen levels has been found to be a risk factor for coronary artery disease[12,13] and myocardial infarction.[14] Increased serum fibrinogen was also shown to be a long-term predictor of ischemic heart disease.[15]

It has been shown that serum albumin is associated with atherosclerosis.[16] Also, serum albumin is a significant inhibitor of platelet activation and aggregation, and mediator of platelet-induced coronary artery disease.[17-19] Hypoalbuminemia has been known as an independent risk factor for coronary artery disease.[20,21] In addition, hypoalbuminemia independently predict poor short or long-term survival after CABG.[22,23]

Fibrinogen-to-albumin ratio (FAR) is a recently introduced prognostic marker and elevated FAR has been reported to be related to worse outcome in patients with acute myocardial

infarction receiving percutaneous coronary intervention (PCI).[24-27] However, to the best of our knowledge, the association between mortality and FAR in patients undergoing coronary artery bypass grafting has not been reported. Therefore, we aimed to investigate the relationship between all-cause mortality and FAR in off-pump coronary artery bypass grafting (OPCAB) patients.

Methods

Study population

This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (approval number 2003-139-1110). Written informed consent was waived because this was a retrospective study. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Electronic medical records of patients who underwent OPCAB at Seoul National University Hospital between March 2006 and December 2016 were reviewed retrospectively. The exclusion criteria were described as follows; Patients with autoimmune disease or treated with steroid, co-operation with other major surgery, lack of data on preoperative fibrinogen or albumin levels. A single surgeon performed all procedures during the study period. All patients were followed up at 1, 3, and 6 months after discharge, and every 3-6 months thereafter.

Data collection

Patients information about medical history, clinic-pathological features including demographic data, comorbidities, medications, laboratory profiles, intraoperative anesthesia records, and postoperative recovery records were obtained from electronic medical records. We matched our institutional database to the nationwide official data on death certification offered by the National Statistical Office.

The primary outcome was the association between preoperative FAR and all-cause mortality in OPCAB patients. According to previous studies, the FAR was defined as the concentration ratio of fibrinogen (mg/dL) to albumin (mg/dL) multiplied by 100.[24,28]

Secondary outcomes were the associations between FAR and cardiovascular mortality and major adverse cardiac event (MACE). We defined cardiovascular mortality as death due to myocardial infraction, heart failure, cardiac arrhythmia, stroke or other vascular causes. Myocardial infarction was defined as followings; (i) cardiac troponin values >10 times the 99th percentile upper normal limit, (ii) new pathological Q waves (iii) angiographic documented new graft or new native coronary artery occlusion, and (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[29] Revascularization was defined as surgery or intervention caused by a thrombosis or occlusion of the graft after OPCAB. MACE was defined as the all-cause mortality, myocardial infarction, and revascularization.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Software, Chicago IL, USA), GraphPad Prism 8 (GraphPad Software, San Diego, CA) and R software (version 3.4.3; R Development Core Team, Vienna, Austria). All data were expressed as means ± standard deviation (SD) or median with interquartile interval (IQR) for continuous variables and as frequencies and percentages for categorical variables. Continuous variables were compared with the unpaired t and Mann-Whitney tests. Categorical variables were compared using the Fisher test or chi-square test. Multiple imputation was used to address missing data (mice R package, m=5).

To evaluate the association between FAR and all-cause mortality in OPCAB patients, patients were divided into 4 groups based on baseline FAR quartile (Q1, <7.33; Q2, 7.33~8.88; Q3, 8.89~10.95; Q4, ≥10.96). To compare baseline data between the quartiles, 1-way analysis of variance (ANOVA) or Kruskal-Wallis test was used for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. The cumulative

survival rate was compared with the Kaplan–Meier curve and the log–rank test according to FAR quartile. A p value of <0.05 was assumed to be statistically significant.

Cox proportional hazards regression models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for each factor. HR was adjusted for covariates related to FAR level or cardiovascular outcome. The lowest preoperative FAR quartile was used as a reference group and FAR was analyzed as a categorized variable. Another cox regression model with continuous FAR without categorized FAR was also performed, because continuous FAR was also significant variable in the univariable analysis. The following predictor variables were included in the univariable analysis of all–cause mortality; age, sex, body mass index (BMI), former smoker, hypertension, diabetes mellitus, history of stroke, dyslipidemia, chronic kidney disease, prior myocardial infarction, emergency operation, use of aspirin, clopidogrel, statin, beta blocker, angiotensin converting enzyme inhibitor and angiotensin II receptor blockers, preoperative hematocrit, serum creatinine, estimated glomerular filtration rate (GFR), high sensitivity C–reactive protein (hs–CRP), preoperative left ventricular ejection fraction (EF), duration of anesthesia, intraoperatively administered crystalloid and packed red blood cells, preoperative FAR as quartiles or continuous variables. The variables found to be significant in the univariable model ($p<0.10$) were included in the multivariable Cox model. If there was a collinearity between two variables, which was assessed by whether variance inflation factor is over 10, the variable with higher HR was chosen. For fibrinogen and albumin, these two variables were excluded from cox regression model to avoid collinearity with preoperative FAR.

The restricted cubic spline function curves of the multivariable–adjusted relationship between preoperative FAR and the relative hazard for all–cause mortality was drawn to evaluate the continuous relationship between FAR and the risk of all–cause

mortality.

To ensure intergroup compatibility between higher and lower FAR group, A propensity score analysis was conducted to match the patient with higher FAR (quartile 4: FAR≥10.96) with the remaining patients with lower FAR (FAR<10.96) to compare the cumulative survival rate in the matched cohort. Cox regression analysis was used to determine the probability of assignment for the 2 FAR groups. This probability and a greedy method with 1:1 pair were used for matching. A total 377 patients with FAR≥10.96 were matched with those with FAR<10.96 using the nearest neighbor matching. The following variables were used as the contributors to the propensity score: age, sex, body mass index, prior myocardial infarction, hypertension, diabetes mellitus, stroke history, dyslipidemia, chronic kidney disease, maintenance of aspirin, maintenance of clopidogrel, maintenance of statin, preoperative hematocrit, preoperative creatinine, preoperative GFR, hs-CRP, preoperative left ventricular EF, duration of surgery, intraoperative crystalloid, colloid and number of RBC use. The caliper was defined as 0.1 standard deviations of the logit-transformed propensity score. The balance between the groups was tested using a standardized difference (>0.20 suggest imbalance). The adjusted cumulative survival rate was compared with the Kaplan-Meier curve and the stratified log-rank test.

Results

A total of 1759 patients was initially enrolled and 37 patients excluded according to the exclusion criteria; patients with important data missing (n=23), autoimmune disease or treated with steroid (n=8), and co-operation with other major surgery (n=6). Ultimately, 1722 patients were enrolled (Figure 1).

Demographic and clinical parameters according to FAR quartile are presented in Table 1. The median follow-up duration was 46 months (IQR, 14-82 months). The Kaplan-Meier time-to-event curve for all-cause mortality is presented in Figure 2. The all-cause mortality was significantly different among FAR quartiles (p <0.001), with graded increases in the all-cause mortality (Q1 vs Q2, p=0.05; Q2 vs. Q3, p =0.027; Q3 vs Q4, p <0.001). The Kaplan-Meier curve for cardiovascular mortality and MACE are presented in Supplemental Figure 1 and 2. Incidence of cardiovascular mortality and MACE were significantly different among FAR quartiles (both p <0.001). Incidence of cardiovascular mortality and MACE in patients with higher FAR quartile (Q4) were significantly higher than those with lower FAR quartile (Q1, both p <0.001 and Q2, both p <0.001).

The results of both univariable and multivariable analyses of risk factors for all-cause mortality are presented in Table 2. Preoperative FAR was a significant risk factor for all-cause mortality both as quartiles and continuous variable. The quartiles of the preoperative FAR showed graded increase in the risk of all-cause mortality at 3rd quartile (HR, 1.740; 95% CI: 1.002-3.023, p=0.040) and 4th quartile (HR, 1.933; 95% CI: 1.129-3.310, p=0.016) compared to 1st quartile. In another cox regression model with continuous FAR, FAR was also a significant risk factor of all-cause mortality as a continuous variable (HR, 1.050; 95% CI: 1.015-1.086, p=0.004). Other significant risk factors for all-cause

mortality included age, diabetes mellitus, previous history of stroke, decreased GFR, elevated hs-CRP, and decreased left ventricular EF. Preoperative aspirin use was associated with decreased risk of all-cause mortality.

The results of both univariable and multivariable analyses of risk factors for cardiovascular mortality and MACE are presented in Supplemental Table 1 and 2. Preoperative FAR quartile was a significant risk factor for cardiovascular mortality in univariable analysis, but was not included in multivariable model. Also, preoperative FAR continuous variable was a significant risk factor for cardiovascular mortality (HR, 1.094; 95% CI: 1.055-1.134, p<0.001) and MACE (HR, 1.075; 95% CI: 1.055-1.095, p<0.001) only in univariable analysis.

The restrictive cubic spline function curve of the multivariable-adjusted relationship between preoperative FAR and the risk of all-cause mortality is shown in Figure 3. As the FAR increased, a gradual increase in relative hazard for all-cause mortality was observed.

Propensity score analysis of preoperative FAR yielded 377 pairs of FAR <10.96 and FAR≥10.96 (Table 3). After propensity score matching, the 2 groups were comparable for all covariates with a standardized difference less than 0.20 (Figure 4). The all-cause mortality was significantly different between two matched groups (p=0.03). The incidence of MACE was also significantly different between two groups (p=0.04), while the cardiovascular mortality was not significantly different between two groups (p=0.8). The Kaplan-Meier curve for all-cause mortality, cardiovascular mortality, and incidence of MACE are presented in Supplemental Figure 3, 4 and 5.

Tables

Table 1. Baseline characteristics of patients according to fibrinogen to albumin ratio quartile.

	FAR <7.33 (n=431)	7.33≤FAR<8.89 (n=430)	8.89≤FAR<10.95 (n=431)	10.95≤FAR (n=430)	Total (n=1722)
Sex, male	302(70.1)	309(71.9)	299(69.4)	314(73)	1224(71)
Age (years)	65(57-71)	67(59-72)	68(61-73)	68(61-73)	67(59-72)
BMI (kg/m^2)	24.8(22.9-26.8)	24.3(22.3-26.4)	24.3(22.8-26.7)	23.9(21.8-26.1)	24.3(22.5-26.5)
Comorbidities at surgery					
Smoking (pack year)	165(37.8)	181(42.1)	164(38.1)	163(37.9)	67.1(38.9)
Hypertension	250(58.0)	286(66.5)	275(63.8)	301(70.0)	1197(69.5)
Diabetes	174(40.4)	195(45.3)	207(48)	253(58.8)	829(48.1)
History of stroke	47(10.9)	48(11.2)	53(12.3)	69(16.0)	217(12.6)
Dyslipidemia	175(40.6)	161(37.4)	130(30.2)	125(29.1)	486(28.2)
Chronic kidney disease	135(31.3)	139(32.3)	149(34.6)	183(42.6)	606(35.2)
Previous myocardial infarction	46(10.7)	51(11.9)	68(15.8)	75(17.4)	240(13.9)
Previous cardiac surgery	9(2.1)	7(1.6)	12(2.8)	4(0.9)	32(1.9)
Prior CABG	14(3.2)	6(1.4)	11(2.6)	4(0.9)	35(2.0)
Involved coronary arteries					
1	13(3.0)	20(4.7)	11(2.6)	11(2.6)	55(3.1)
2	60(13.9)	52(12.1)	62(14.4)	31(7.2)	205(11.7)
3	331(76.8)	322(74.9)	319(74)	346(80.5)	1318(74.9)
Emergency operation	3(0.7)	5(1.2)	9(2.1)	15(3.5)	32(1.9)
Preoperative medication					
Aspirin	245(56.8)	249(57.9)	224(52)	192(44.7)	910(52.8)
Clopidogrel	126(29.2)	129(30.0)	121(27.8)	108(25.1)	483(28.0)
Statin	208(48.3)	208(48.4)	221(51.3)	197(45.8)	834(48.4)
Beta blocker	73(16.9)	73(17.0)	83(19.3)	81(18.8)	310(18.0)
ACEi	45(10.4)	61(14.2)	65(15.1)	89(20.7)	260(15.1)
ARB	52(12.1)	68(15.8)	71(16.5)	77(17.9)	268(15.6)
Preoperative laboratory value					
Fibrinogen (mg/dL)	273(246-290)	328(311-343)	383(361-404)	498.5(458-573)	377(320-460)
Albumin (g/dL)	4.25(4.0-4.5)	4.0(3.8-4.1)	3.9(3.7-4.1)	3.6(3.3-3.8)	3.9(3.6-4.1)
FAR	6.4(5.9-6.9)	8.2(7.7-8.5)	9.8(9.3-10.4)	13.3(11.9-15.6)	8.9(7.3-11.0)
Hematocrit (%)	33(30-37)	33(30-37)	32(29-36)	32(28-36)	
Estimated GFR (ml/min/1.73m^2)	73.7(58.8-94.6)	72.3(55.4-89.7)	65.1(49.5-85.1)	56.9(35.7-76.5)	67.4(50.4-86.6)
hs-CRP (mg/dL)	0.09(0.03-0.23)	0.18(0.06-0.50)	0.37(0.14-0.82)	0.94(0.34-2.84)	0.26(0.08-0.78)
Ejection fraction (%)	58.5(53-63)	58(51-64)	57(49-63)	55(43-62)	57(50-63)
Operative variables					
Anesthesia duration (min)	440(395-475)	435(400-480)	440(400-480)	445(400-490)	440(400-480)
Operation duration (min)	364.5(321-400)	360(325-400)	365(325-410)	370(330-410)	365(325-405)
Crystalloid (ml)	1400(700-2650)	1375(700-2850)	1350(800-2800)	1300(600-2700)	1400(700-2750)
Colloid (ml)	0(0-800)	0(0-900)	0(0-900)	300(0-1000)	0(0-900)
pRBC	0(0-2)	1(0-2)	0(0-2)	0(0-2)	0(0-2)

The values are expressed as the median (interquartile range) or number (%)

BMI, body mass index; CABG, coronary artery bypass graft surgery; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; FAR, fibrinogen to albumin ratio; GFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; pRBC, packed red blood cells

Table 2. Multivariable Cox regression analysis for all-cause mortality after off-pump coronary artery bypass grafting.

Variables	Hazard ratio	95% confidence interval	*p* value
Age (years)	1.064	1.044-1.084	<0.001
BMI (kg/m^2)	0.957	0.907-1.009	0.101
Hypertension	1.093	0.756-1.581	0.637
Diabetes mellitus	1.370	1.004-1.869	0.047
Stroke history	1.868	1.309-2.666	0.001
Chronic kidney disease	1.106	0.815-1.503	0.517
Emergency operation	0.726	0.250-2.108	0.556
Aspirin	0.719	0.524-0.988	0.042
Clopidogrel	1.074	0.754-1.531	0.691
Statin	0.727	0.529-0.999	0.050
Beta blocker	1.283	0.923-1.7820	0.138
ACEi	0.877	0.599-1.285	0.501
Preoperative laboratory value			
Estimated GFR (ml/min/1.73m^2)	0.982	0.976-0.989	<0.001
hs-CRP (mg/dL)	1.077	1.019-1.139	0.008
Left ventricular EF (%)	0.969	0.956-0.982	<0.001
Operative variables			
Operation time	0.999	0.996-1.001	0.233
Preoperative FAR			
Quartile 1, FAR <7.33	Baseline		
Quartile 2, 7.33≤FAR<8.89	1.347	0.756-2.400	0.355
Quartile 3, 8.89≤FAR<10.96	1.740	1.002-3.023	0.040
Quartile 4, 10.96≤FAR	1.933	1.129-3.310	0.016

The variables found to be significant in the univariable model ($p<0.10$) were included in the multivariable Cox model.

BMI, body mass index; ACEi, angiotensin converting enzyme inhibitor; GFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; EF, ejection fraction; FAR, fibrinogen to albumin ratio

Table 3. Patient characteristics and perioperative parameters between the patients with FAR quartile 4 (≥10.96) and the patients with FAR quartile 1~3 (<10.96) after propensity score matching.

Variables	Before Matching		Standardized Difference	After Matching		Standardized Difference
	FAR Quartile 1-3 (n=1288)	FAR Quartile 4 (n=433)		FAR Quartile 1-3 (n=377)	FAR Quartile 4 (n=377)	
Demographic data	-	-	-	-	-	-
Sex, male	907(70.4)	314(73)	0.020	275(72.9)	275(72.9)	0.000
Age (years)	67(59-72)	68(61-73)	0.209	68(60-73)	68(61-73)	0.028
BMI (kg/m^2)	24.5(22.7-26.6)	23.9(21.8-26.1)	0.165	23.7(22.1-25.7)	24.0(22.2-26.3)	0.102
Past medical history	-	-	-	-	-	-
Hypertension	870(67.5)	324(75.3)	0.194	280(74.3)	280(74.3)	0.000
Diabetes mellitus	573(44.5)	253(58.8)	0.200	213(56.5)	219(58.1)	0.032
Stroke history	148(11.5)	69(16.0)	0.167	65(17.2)	61(16.2)	0.029
Prior myocardial infarction	165(12.8)	75(17.3)	0.125	62(16.4)	60(15.9)	0.014
Dyslipidemia	377(29.3)	125(29.1)	0.082	184(48.8)	181(48.0)	0.015
Chronic kidney disease	420(32.6)	183(42.6)	0.146	163(43.2)	157(41.6)	0.032
Aspirin	717(55.7)	192(44.7)	0.218	181(48.0)	179(47.5)	0.010
Clopidogrel	374(29.0)	108(25.1)	0.078	89(23.6)	98(26.0)	0.055
Statin	634(68.8)	197(45.8)	0.249	178(47.2)	180(47.7)	0.010
Preoperative variables	-	-	-	-	-	-
Hematocrit (%)	33(30-37)	32(28-36)	0.169	32(28-36)	32(28-36)	0.013
Creatinine (mg/dL)	1.0(0.8-1.2)	1.0(0.9-1.2)	0.081	1.0(0.9-1.2)	1.0(0.9-1.2)	0.041
Estimated GFR (ml/min/1.73m^2)	70.7(54.3-89.4)	56.9(35.7-76.5)	0.372	60.4(45.5-80.3)	57.5(39.8-76.5)	0.028
hs-CRP (mg/dL)	0.2(0.1-0.5)	0.94(0.34-2.84)	0.546	0.4(0.1-1.3)	0.7(0.3 -1.9)	0.028
Ejection fraction (%)	58(52-63)	55(43-62)	0.257	56(42-62)	56(43-63)	0.030
Operative variables	-	-	-	-	-	-
Operation time (min)	360(325-405)	370(330-41)	0.133	370(335-415)	370(330-410)	0.023
Intraoperative crystalloid (ml)	1400(700-2760)	1300(600-2700)	0.049	1400(700-2800)	1400(600-2700)	0.030
Intraoperative colloid (ml)	0(0-812.5)	0(300-1000)	0.104	0(0-1000)	200(0-1000)	0.009
Intraoperative pRBC	0(0-2)	0(0-2)	0.035	1(0-2)	0(0-2.7)	0.081

The values are expressed as the median (interquartile range) or number (%).

Quartiles 1, 2, 3, and 4 are the 0 to 25th, 25th to 50th, 50th to 75th, and 75th to 100th percentiles; Quartile 1, FAR <7.33; Quartile 2, 7.33≤FAR<8.89; Quartile 3, 8.89≤FAR<10.96; Quartile 4, 10.96≤FAR

FAR, fibrinogen to albumin ratio; BMI, body mass index; GFR, glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; pRBC, packed red blood cells

Figures

Figure 1. Flow diagram of the study. OPCAB, off-pump coronary artery bypass grafting

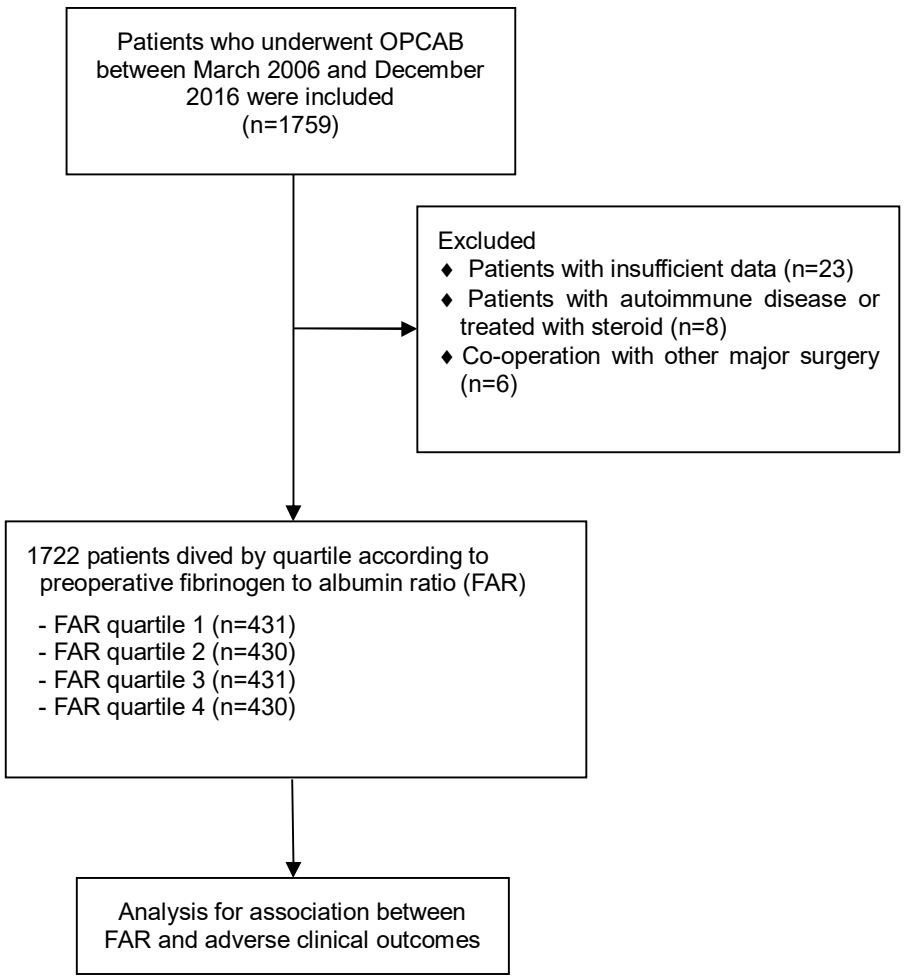


Figure 2. Kaplan-Meier time-to-event curve for all-cause mortality according to preoperative FAR quartile following off-pump coronary artery bypass grafting. FAR, fibrinogen to albumin ratio

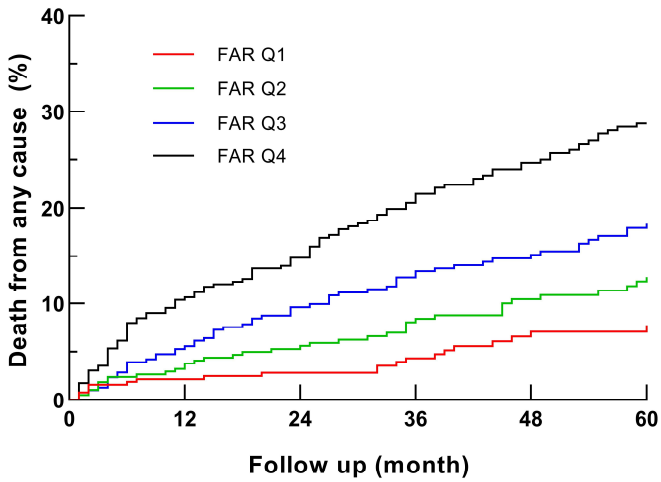


Figure 3. Restricted cubic spline curve of the multivariable-adjusted relationship between preoperative fibrinogen to albumin ratio (FAR) and the hazard for all-cause mortality in off-pump coronary artery bypass grafting patients, with the median value of FAR quartile 1 (FAR = 6.4) as the reference value. The shaded area represents the 95% confidence interval.

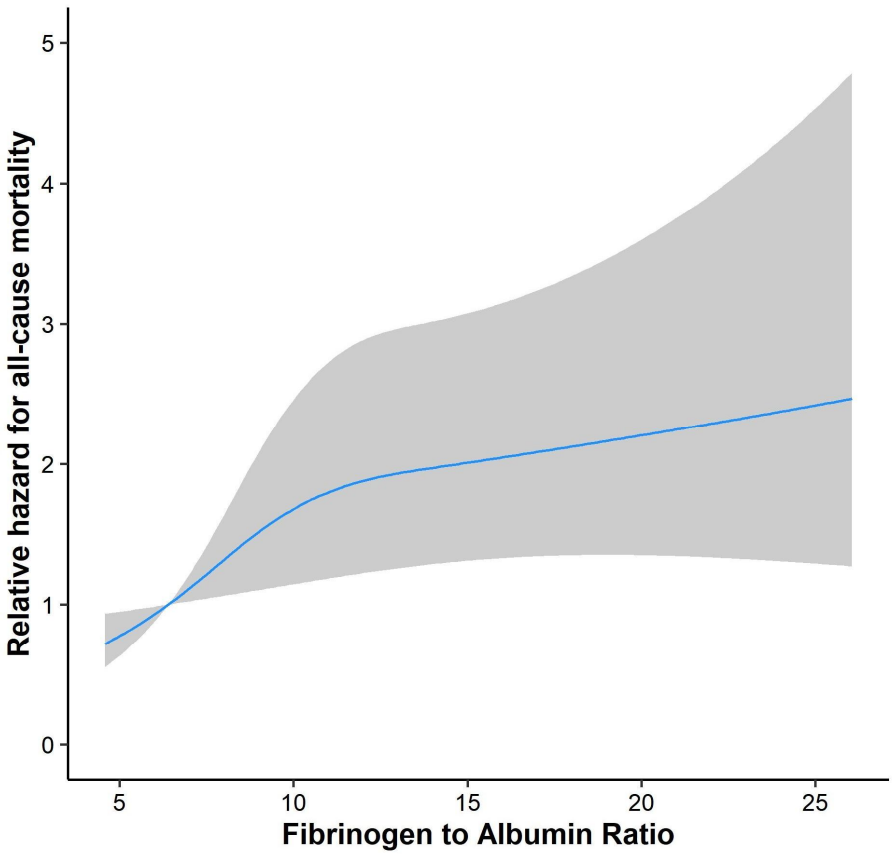
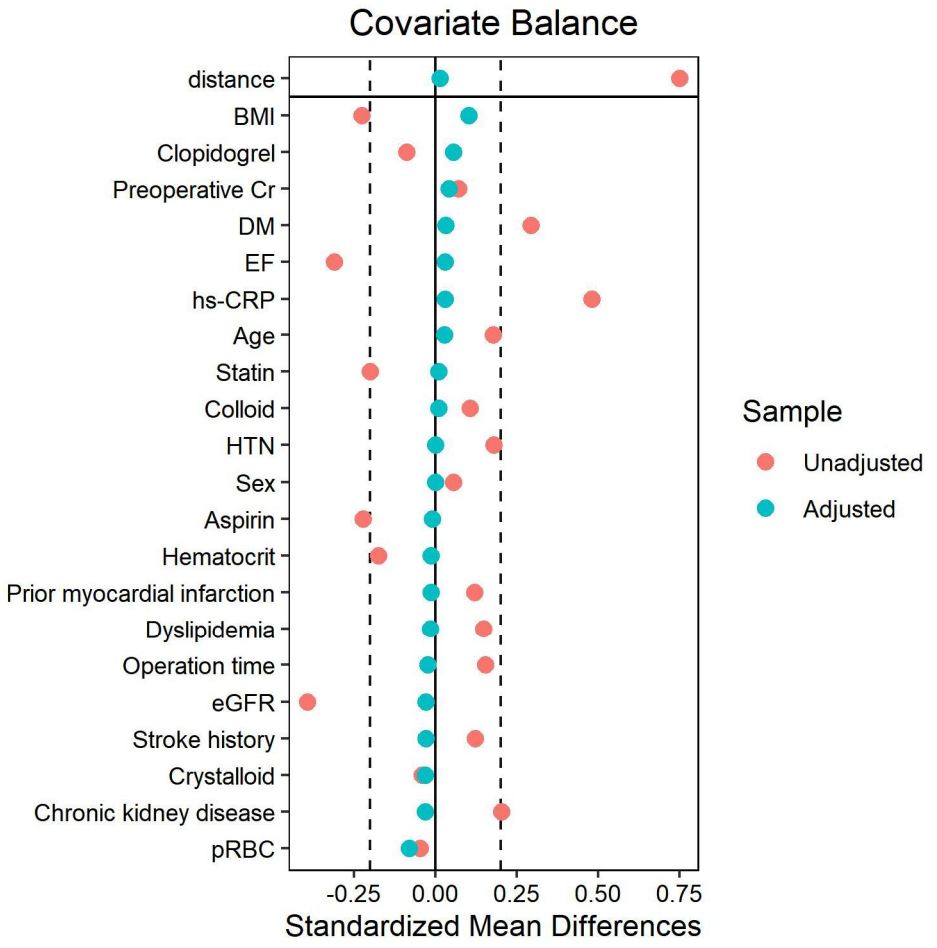


Figure 4. Covariate balance plot before after propensity score matching. BMI, body mass index; Cr, creatinine; DM, diabetes mellitus; EF, left ventricular ejection fraction; hs-CRP, high sensitivity C-reactive protein; HTN, hypertension; eGFR, estimated glomerular filtration rate; pRBC, packed red blood cells



Supplemental tables

Supplemental Table 1. Multivariable Cox regression analysis for cardiovascular mortality after off-pump coronary artery bypass grafting.

Variables	Hazard ratio	95% confidence interval	*p* value
Age (years)	1.048	1.019-1.078	0.001
BMI (kg/m^2)	0.956	0.880-1.040	0.296
Aspirin	0.389	0.224-0.673	0.001
Statin	0.666	0.403-1.099	0.112
Preoperative laboratory value			
Hematocrit (%)	0.973	0.927-1.021	0.262
Estimated GFR (ml/min/1.73m^2)	0.979	0.969-0.988	<0.001
hs-CRP (mg/dL)	1.067	0.994-1.146	0.075
Left ventricular EF (%)	0.964	0.947-0.981	<0.001
Preoperative FAR			
Quartile 1, FAR <7.33	Baseline		
Quartile 2, 7.33≤FAR<8.89	1.199	0.488-2.947	0.693
Quartile 3, 8.89≤FAR<10.96	1.570	0.678-3.635	0.293
Quartile 4, 10.96≤FAR	1.591	0.699-3.622	0.269

The variables found to be significant in the univariable model (p<0.10) were included in the multivariable Cox model.

BMI, body mass index; GFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; EF, ejection fraction; FAR, fibrinogen to albumin ratio

Supplemental Table 2. Multivariable Cox regression analysis for major adverse cardiac event (MACE) after off-pump coronary artery bypass grafting.

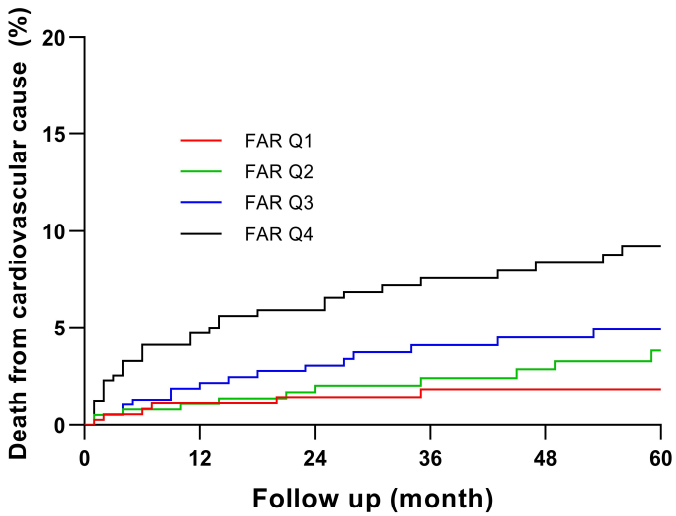
Variables	Hazard ratio	95% confidence interval	*p* value
Age (years)	1.047	1.033-1.062	<0.001
BMI (kg/m^2)	0.946	0.908-0.986	0.008
Aspirin	0.791	0.626-0.999	0.049
Statin	0.847	0.671-1.070	0.163
Preoperative laboratory value			
Hematocrit (%)	0.997	0.969-0.986	0.784
Estimated GFR (ml/min/1.73m^2)	0.991	0.986-0.995	<0.001
hs-CRP (mg/dL)	1.088	1.046-1.131	<0.001
Left ventricular EF (%)	0.977	0.969-0.986	<0.001
Preoperative FAR			
Quartile 1, FAR <7.33	Baseline		
Quartile 2, 7.33≤FAR<8.89	0.915	0.632-1.323	0.636
Quartile 3, 8.89≤FAR<10.96	1.046	0.733-1.492	0.805
Quartile 4, 10.96≤FAR	1.278	0.909-1.799	0.159

The variables found to be significant in the univariable model (p<0.10) were included in the multivariable Cox model.

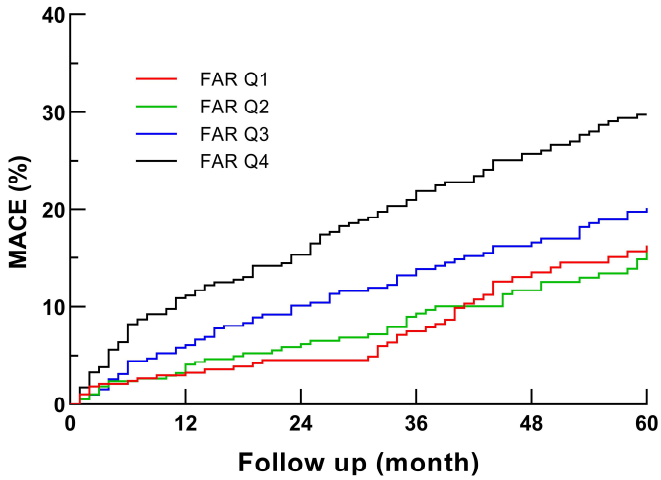
BMI, body mass index; GFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; EF, ejection fraction; FAR, fibrinogen to albumin ratio

Supplemental figures

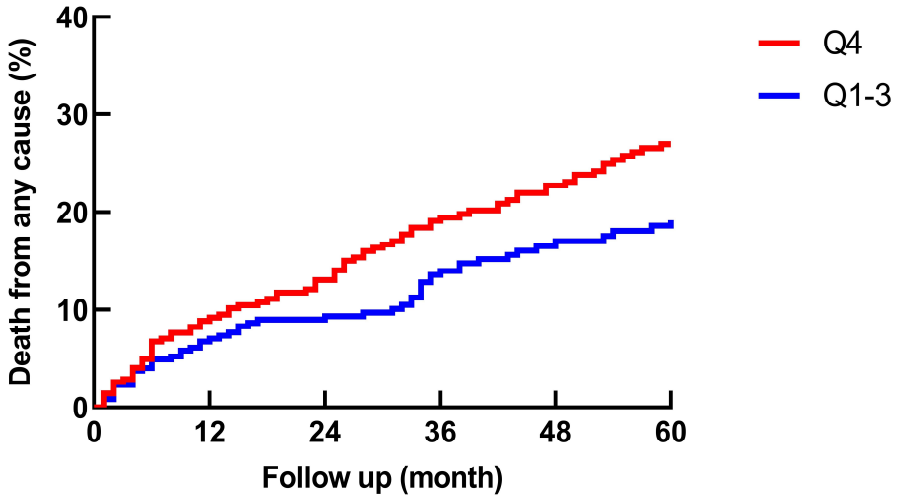
Supplemental Figure S1. Kaplan–Meier time–to–event curve for cardiovascular mortality according to preoperative FAR quartile. FAR, fibrinogen to albumin ratio



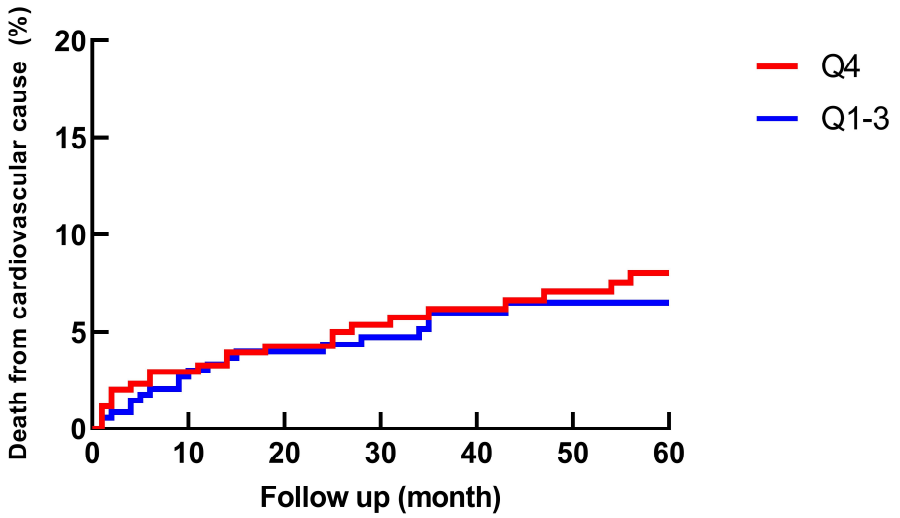
Supplemental Figure S2. Kaplan–Meier time–to–event curve for MACE according to preoperative FAR quartile. FAR, fibrinogen to albumin ratio



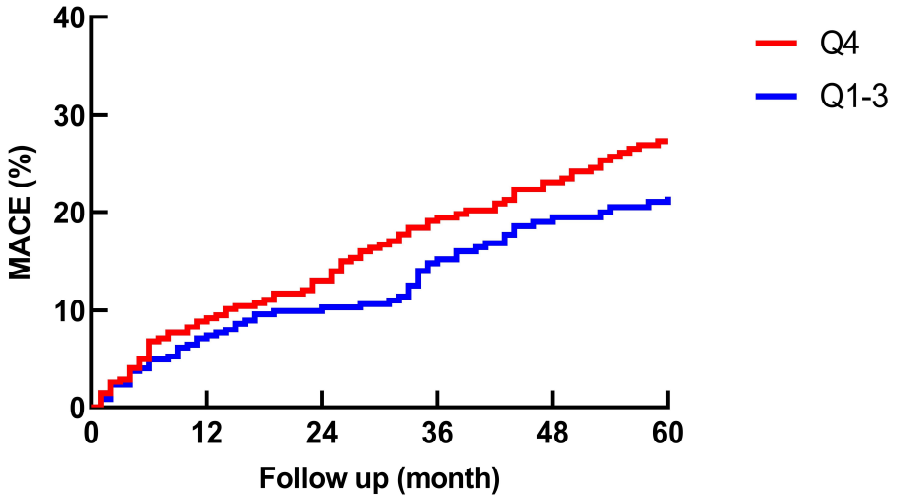
Supplemental Figure S3. Kaplan-Meier time-to-event curve for all-cause mortality between low FAR (quartile 1~3) and high FAR (quartile 4) after propensity score matching. FAR, fibrinogen to albumin ratio



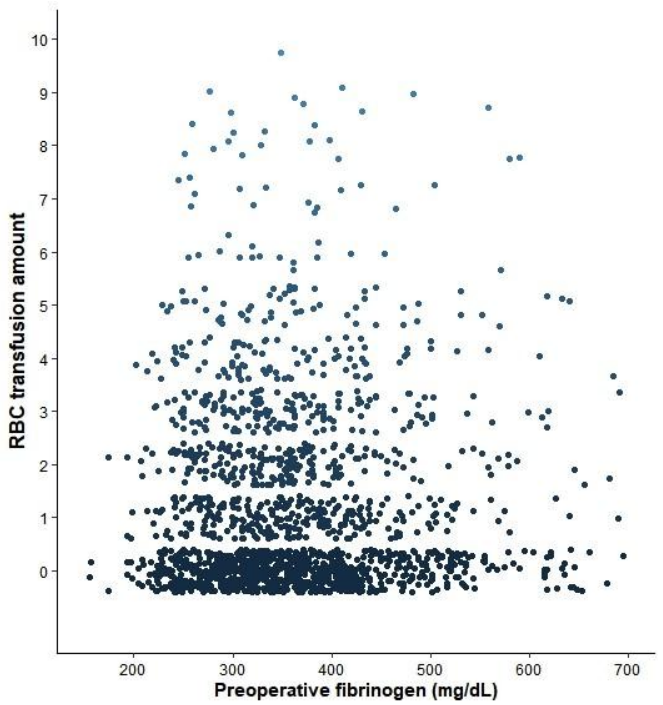
Supplemental Figure S4. Kaplan-Meier time-to-event curve for cardiovascular mortality between low FAR (quartile 1~3) and high FAR (quartile 4) after propensity score matching. FAR, fibrinogen to albumin ratio



Supplemental Figure S5. Kaplan-Meier time-to-event curve for MACE curve between low FAR (quartile 1~3) and high FAR (quartile 4) after propensity score matching. FAR, fibrinogen to albumin ratio



Supplemental Figure S6. Scatter plot of preoperative fibrinogen and intraoperative red blood cell transfusion amount. RBC, red blood cell



Discussion

In this retrospective study, we evaluated the association between preoperative FAR and all-cause mortality in OPCAB patients. Elevated preoperative FAR was significantly associated with an increased risk of death from any cause after OPCAB. As preoperative FAR increased, the hazard of all-cause mortality gradually increased across the quartiles. After propensity score matching for other variables, the all-cause mortality was significantly higher in patients in the fourth quartile of FAR compared with those in the remaining quartiles. To the best of our knowledge, this is the first study that report the relationship between FAR and outcomes after cardiac surgery.

FAR was reported to be associated with worse prognosis in patients with acute myocardial infarction who received PCI,[24-27] and also significantly associated with the severity of stable coronary artery disease (CAD).[30] In addition, FAR was associated with postoperative mortality in cancer patients such as breast cancer and stomach cancer[28,31] As both low serum albumin and high serum fibrinogen are associated with atherosclerosis and inflammatory response,[12,20,21] elevated FAR seems to be associated with atherosclerosis, high plasma viscosity and thrombus tendency, which contribute to poor prognosis.[26] Furthermore, serum albumin is not only an indicator of the systemic inflammatory response, it is also an indicator of the nutritional status that is important for patient prognosis. Therefore, elevated FAR in patients receiving OPCAB may reflect the nutritional status and inflammatory process in the atherosclerosis progression and predicts postoperative prognosis.

Most of the studies dealing with FAR were performed under non-surgical conditions or under surgery with minimal blood loss. In contrast, bleeding risk could be increased in low fibrinogen concentration status in cardiac surgery and also in OPCAB[32-35].

Recent studies have found U-shaped relationship between preoperative fibrinogen level and severe perioperative bleeding in cardiac surgery patients, which means both low and high fibrinogen level were associated with increased risk of perioperative bleeding.[36] In this study, however, we could not find specific correlation between preoperative fibrinogen level and intraoperative red blood cell (RBC) transfusion amount in our study population (Supplemental Figure 6). We only included off-pump CABG cases and intraoperative RBC transfusion rate was low, about half of cases without transfusion and only 3.9% cases requiring RBC over 5 units, thus it should be interpreted with caution Fibrinogen supplementation is widely used in cardiac surgery to reduce intraoperative bleeding, while its benefit is yet controversial.[37-41] Reduction in perioperative blood loss was remarkable only in the specific subgroup with high risk of blood loss.[32,42-44] Although preoperative fibrinogen supplementation reduced blood loss and transfusion rate in few studies, it did not bring improvement in clinically relevant outcomes.[45,46] Furthermore, even some studies reported increase in transfusion rate in fibrinogen supplementation group[47,48] or higher preoperative fibrinogen level.[49] Contrary to preoperative fibrinogen level, hazard ratio of FAR for all-cause mortality increased along the FAR quartiles in our study, which shows that preoperative FAR could be a more reliable prognostic factor than fibrinogen, alone.

Nevertheless, our study should be interpreted under several limitations. First, the present study is a single-center, retrospective cohort study. Thus, whether interventions to change FAR could improve the outcomes remains unclear. In addition, although we performed propensity score matching for variables other than FAR, selection bias might exist even with this method because of this study's retrospective nature. Further prospective study is required to validate a definitive conclusion regarding clinical application of FAR and its optimal cut-off for predicting risk

in CABG patients. Second, we only studied the initial preoperative FAR value. Changes of FAR over time may provide additional prognostic information. Whether postoperative FAR level have predictive value remains unclear, either. Third, we only included patients treated with off-pump CABG. Therefore, further studies are required to assess prognostic role of preoperative FAR for cardiac surgeries that undergo cardiopulmonary bypass. Fourth, this study was performed as a single-center retrospective study, so we could not include external validation cohort to verify our findings. Therefore, further studies are still required to confirm the role of FAR in predicting survival after OPCAB.

Conclusion

In summary, higher FAR was associated with increased all-cause mortality after OPCAB. Preoperative FAR could be a prognostic factor for predicting higher mortality after OPCAB.

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초 록

무체외순환 관상동맥우회술을 받는 환자에서 수술 전 피브리노겐과 알부민의 비율이 사망률에 미치는 영향: 후향적 관찰연구

피브리노겐·알부민 비는 최근 관상동맥질환과 관련 있는 예후인자로 소개되었다. 본 연구는 무체외순환 관상동맥우회술을 받는 환자에서 수술전 피브리노겐·알부민 비가 수술 후 임상적인 예후와 연관성이 있는지를 알아보고자 한다.

2006년 3월부터 2016년 12월까지 무체외순환 관상동맥우회술을 받은 1759명의 환자들을 대상으로 하였으며, 수술 전 피브리노겐·알부민 비의 사분위에 따라 4군으로 나누었다. 콕스회귀분석을 통해 피브리노겐·알부민 비와 사망률의 연관성을 분석하였으며 성향점수 매칭을 통해 피브리노겐·알부민 비가 높은 군과 낮은 군으로 매칭하여 피브리노겐·알부민 비와 사망률 간의 연관성을 분석하였다.

콕스회귀분석을 통해 수술전 피브리노겐·알부민 비가 무체외순환 관상동맥우회술을 받은 환자의 사망에 독립적인 위험인자임을 확인하였으며 성향점수 매칭 후 피브리노겐·알부민 비가 가장 높은 군과 나머지 군 사이에서도 유의한 결과를 확인할 수 있었다.

높은 피브리노겐·알부민 비는 무체외순환 관상동맥우회술 후의 사망률과 연관되어 있으며 수술 전 피브리노겐·알부민 비가 높을 경우 무체외순환 관상동맥우회술 이후의 높은 사망률을 예측하는 예후인자가 될 수 있을 것으로 생각된다.

주요어 : 피브리노겐·알부민 비, 피브리노겐, 알부민, 무체외순환 관상동맥우회술

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