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Association between glucose-to-lymphocyte ratio and long-term mortality among women after coronary artery bypass grafting: filling gaps in female

Kai Zhang[1], Rong Zhang[1], Maoxun Huang[1] and Bo Li[1*]

Abstract

Background Inflammation plays a pivotal role in the progression of coronary artery disease and increases the risk of mortality in patients undergoing coronary artery bypass grafting (CABG). The glucose-to-lymphocyte ratio (GLR), calculated from serum glucose levels and peripheral lymphocyte counts, is a novel marker of inflammation, but its relationship with outcomes after CABG remains unexplored. The aim of this study was to evaluate the association between GLR and long-term mortality.

Methods This retrospective cohort study used data from the Medical Information Mart for Intensive Care (MIMIC) database to examine baseline and outcome data for CABG patients. Participants were stratified into quartiles based on GLR levels, and the Cox proportional hazards model and restricted cubic spline analysis were used to evaluate the association between GLR and mortality.

Results A total of 592 adult patients (mean age 70.0 ± 10.3 years, mean BMI 30.6 ± 6.8 kg/m^2) were included. After multivariable adjustment, patients in the highest quartile of GLR had a hazard ratio (HR) of 3.3 (95% CI: 1.04–10.49; Q4 vs. Q2), while those in the lowest quartile had a HR of 5.62 (95% CI: 1.71–18.48; Q1 vs. Q2). A U-shaped relationship was observed between GLR and risk of death (*P* for nonlinearity < 0.05), with sensitivity and subgroup analyses supporting these findings.

Conclusions GLR was significantly associated with an increased risk of long-term mortality, with both the highest and lowest quartiles demonstrating elevated hazard ratios compared to the second quartile. Assessing GLR may have clinical relevance for predicting mortality risk, providing valuable insights for preventive strategies and patient management.

Keywords Glucose-to-lymphocyte ratio, Long-term mortality, Association, Coronary artery bypass grafting, Woman

Introduction

Coronary artery bypass graft (CABG) surgery represents the most frequently performed cardiovascular surgical procedure worldwide [1]. According to guidelines from the United States and Europe, CABG is considered the gold standard of care for patients with complex multivessel coronary artery disease, left main disease, diabetes, or reduced left ventricular function [2, 3]. Despite

*Correspondence:
Bo Li
108985161@qq.com
[1] Jilin University Second Hospital, No. 218, Zi Qiang Street, Changchun, Jilin Province, China

significant advancements in CABG techniques over the past decade, several challenges persist, particularly concerning gender differences in surgical outcomes.

In the United States, more than 370,000 patients undergo CABG each year, with approximately 30% of those being women [4]. Historically, female patients have exhibited consistently higher mortality rates than their male counterparts, underscoring the underappreciated influence of gender on CABG outcomes [5–8]. Although progress has been made in treating coronary artery disease (CAD), improvements in outcomes specifically for women have been limited. This highlights the necessity of considering women as a distinct group in clinical practice and the importance of investigating CABG-specific risk factors pertinent to this population [9–11]. Notably, the identification of clear inflammatory risk factors is essential for effective risk stratification and for guiding treatment decisions for patients.

The glucose-to-lymphocyte ratio (GLR), calculated from serum glucose concentration and peripheral lymphocyte count, serves as a biomarker reflecting both glucose metabolism and systemic inflammation [12–14]. Elevated GLR has been recognized as a predictor of acute mortality and prognosis in several cardiovascular conditions, including acute myocardial infarction [15] and atherosclerotic cardiovascular disease [16]. However, research on the impact of GLR in the context of coronary artery bypass grafting (CABG) is limited; to date, only one study has established a connection between GLR and postoperative acute kidney injury in CABG patients, without exploring long-term outcomes [17]. Additionally, high-quality research focusing on outcomes in high-risk women remains particularly scarce.

Consequently, this study aims to analyze a large national database to evaluate the association between GLR and long-term mortality in female patients undergoing CABG.

Method

Study design and ethics

The data were collected from the Medical Information Mart for Intensive Care, a large US-based critical care database containing high-quality, well-defined data on ICU patients admitted to Beth Israel Deaconess Medical Center [18]. A member of the study team with access to MIMIC performed data extraction using Structured Query Language (SQL) in PostgreSQL. As all patients in the database were de-identified, informed consent was waived. This study adhered to the tenets of the Declaration of Helsinki (1975). The MIMIC database is publicly available and has received Institutional Review Board (IRB) approval from both the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (0403000206).

Cohort selection

Patients diagnosed with coronary artery disease who underwent coronary artery bypass grafting (CABG) and were over 18 years of age at their first ICU admission were included in this study. Eligible patients received standardized surgical care, with operations performed by a senior surgeon [19]. Exclusion criteria were as follows: (1) male patients; (2) missing data on fasting blood glucose and lymphocyte count on the first day of ICU admission; and (3) patients with repeated ICU admissions. Finally, 592 female patients undergoing CABG were included in this study. The detailed selection process is shown in Fig. 1.

Covariate measures

Initial measurements taken within the first 24 h of ICU admission were used as the parameters for this study. To extract patient information, Structured Query Language (SQL) and Navicat software (version 15) were used to retrieve the necessary data. Covariates were selected based on clinical relevance and data availability. The variables analyzed were categorized as follows: (1) demographic factors, including age and body mass index (BMI); (2) vital signs, such as arterial systolic blood pressure (ABPS), arterial diastolic blood pressure (ABPD) and heart rate; (3) comorbidities, including hypertension, diabetes, myocardial infarction, chronic kidney disease, acute renal failure, stroke, hyperlipidemia and chronic obstructive pulmonary disease (COPD); (4) laboratory indicators, including white blood cell (WBC) count, sodium, potassium, total calcium, chloride, anion gap, free calcium, urea nitrogen and creatinine levels; and (5) scoring systems, including Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation III (APS III) scores.

Exposure and outcome

Within 24 h of admission, serum glucose and lymphocyte levels were measured. The glucose-to-lymphocyte ratio (GLR) was calculated using the formula: GLR = glucose (mg/dL) ÷ lymphocyte count (K/μL). Patients were divided into four groups according to the quartiles of the GLR: Q1 (< 41), Q2 (41–57), Q3 (57–80) and Q4 (> 81). Clinical information was collected at the time of ICU admission, and only data from the first ICU admission after the first admission were collected for patients with multiple hospitalizations. The primary outcome of the study was long-term mortality, assessed at two, three, four and five years.

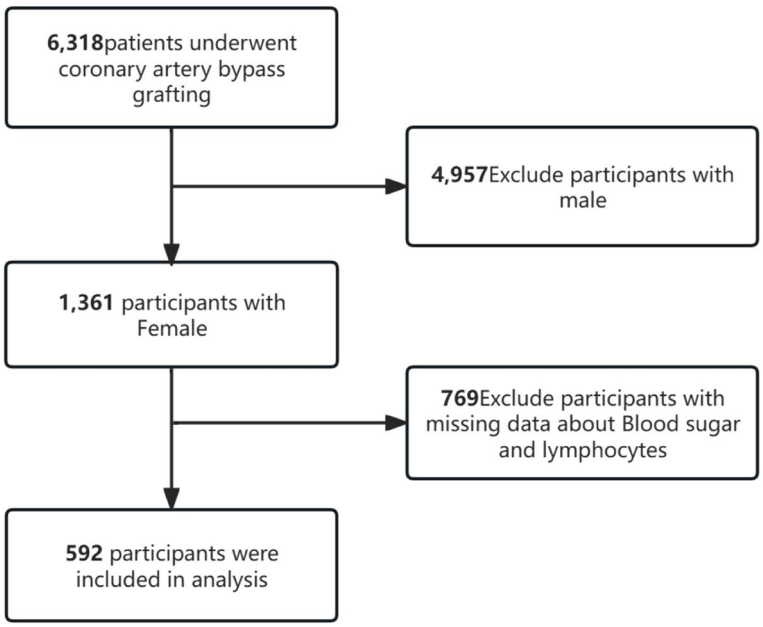

Fig. 1 Flowchart of the study cohort selection criteria

Statistical analyses

Descriptive statistics

Baseline characteristics are reported as mean ± standard deviation (SD) for continuous variables and as number (percentage) for categorical variables. Descriptive statistics for non-normally distributed variables are presented as medians with interquartile ranges (IQR). Baseline differences between groups were evaluated using one-way ANOVA followed by Tukey's post hoc test or the chi-square test as appropriate.

Multivariate analysis

A multivariate Cox proportional hazards model assessed the association between GLR and mortality in female patients across five models: Model 1 (unadjusted), Model 2 (adjusted for demographics), Model 3 (Model 2 plus basic vital signs and comorbidities), Model 4 (additional adjustments for blood biochemical markers), and Model 5 (further adjustments for SOFA and APS III). Linear trends were examined by assigning the median values of GLR quartiles as categorical variables in all models.

Curve fitting and threshold effect

Non-linear relationships between GLR and outcomes were evaluated using restricted cubic spline functions. If non-linearity was observed, a two-piece linear regression model identified threshold effects, with GLR thresholds determined by a recursive method and validated using a maximum likelihood model.

Sensitivity and subgroup analyses

Sensitivity analyses tested the robustness of the results. Stratified analyses examined whether GLR effects differed in subgroups defined by hypertension, type 2 diabetes, heart failure, myocardial infarction, chronic kidney disease, acute renal failure, SOFA, and APS III. Multiplicative interactions were assessed using likelihood ratio tests. Missing data were imputed using the Multivariate Imputation by Chained Equations (MICE) function in R, with predictive mean matching to confirm stability across imputed datasets [20]. MICE generates multiple imputed datasets by constructing a series of regression models for each variable with missing values, utilizing other available variables as predictors. This iterative approach helps to account for the uncertainty inherent in missing data, resulting in the generation of several plausible datasets. We specifically selected the MICE method due to its ability to simultaneously handle both classification and interpolation of continuous variables, which is particularly well-suited for the mixed data characteristics observed in our study. Furthermore, MICE facilitates the modeling of complex relationships and correlations among variables, which is essential for ensuring the comprehensiveness of our analysis.

All analyses were performed using R (version 4.1.1) and Free Statistics software (version 1.8). A two-sided

Table 1 Baseline characteristics of participants

Variables	Total ($n=592$)	Q1 ($n=148$) [b]	Q2 ($n=148$) [b]	Q3 ($n=148$) [b]	Q4 ($n=148$) [b]	*P* value [a]
Age, Mean ± SD	70.0 ± 10.3	67.7 ± 10.7	69.7 ± 10.4	71.2 ± 10.2	71.4 ± 9.8	0.007
BMI, Mean ± SD	30.6 ± 6.8	31.0 ± 7.4	31.6 ± 6.9	30.3 ± 6.5	29.6 ± 6.2	0.066
Vital signs						
heart rate, Mean ± SD	80.8 ± 9.1	82.2 ± 8.9	80.0 ± 8.9	80.2 ± 9.5	80.7 ± 8.9	0.14
ABPS, Mean ± SD	112.6 ± 8.2	111.8 ± 7.3	112.6 ± 8.1	113.1 ± 8.2	112.9 ± 9.3	0.538
ABPD, Mean ± SD	56.1 ± 7.1	56.2 ± 6.4	55.6 ± 7.3	56.3 ± 7.4	56.4 ± 7.3	0.726
comorbidities						
hypertension, n (%)						0.003
No	261 (44.1)	62 (41.9)	54 (36.5)	61 (41.2)	84 (56.8)	
Yes	331 (55.9)	86 (58.1)	94 (63.5)	87 (58.8)	64 (43.2)	
diabetes, n (%)						0.295
No	290 (49.0)	65 (43.9)	70 (47.3)	81 (54.7)	74 (50)	
Yes	302 (51.0)	83 (56.1)	78 (52.7)	67 (45.3)	74 (50)	
myocardial infarct, n (%)						0.607
No	384 (64.9)	97 (65.5)	93 (62.8)	102 (68.9)	92 (62.2)	
Yes	208 (35.1)	51 (34.5)	55 (37.2)	46 (31.1)	56 (37.8)	
chronic kidney disease, n (%)						0.1
No	477 (80.6)	121 (81.8)	124 (83.8)	123 (83.1)	109 (73.6)	
Yes	115 (19.4)	27 (18.2)	24 (16.2)	25 (16.9)	39 (26.4)	
Acute renal failure, n (%)						0.054
No	470 (79.4)	124 (83.8)	116 (78.4)	123 (83.1)	107 (72.3)	
Yes	122 (20.6)	24 (16.2)	32 (21.6)	25 (16.9)	41 (27.7)	
stroke, n (%)						0.769
No	543 (91.7)	138 (93.2)	134 (90.5)	137 (92.6)	134 (90.5)	
Yes	49 (8.3)	10 (6.8)	14 (9.5)	11 (7.4)	14 (9.5)	
hyperlipidemia, n (%)						0.492
No	129 (21.8)	35 (23.6)	26 (17.6)	36 (24.3)	32 (21.6)	
Yes	463 (78.2)	113 (76.4)	122 (82.4)	112 (75.7)	116 (78.4)	
COPD, n (%)						0.763
No	527 (89.0)	130 (87.8)	135 (91.2)	130 (87.8)	132 (89.2)	
Yes	65 (11.0)	18 (12.2)	13 (8.8)	18 (12.2)	16 (10.8)	
Blood biochemical indicators						
WBC, Mean ± SD	14.0 ± 5.2	17.0 ± 6.2	14.7 ± 5.2	12.5 ± 3.4	11.6 ± 3.9	< 0.001
sodium, Mean ± SD	137.7 ± 3.1	137.6 ± 2.7	137.5 ± 3.1	138.1 ± 2.7	137.5 ± 3.6	0.232
potassium, Mean ± SD	4.4 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	4.3 ± 0.4	4.4 ± 0.4	0.034
calcium total, Mean ± SD	8.6 ± 0.7	8.7 ± 0.7	8.5 ± 0.7	8.7 ± 0.6	8.6 ± 0.7	0.167
chloride, Mean ± SD	106.2 ± 3.5	106.4 ± 3.3	106.3 ± 3.6	106.6 ± 3.0	105.6 ± 4.1	0.06
anion gap, Mean ± SD	11.2 ± 2.6	11.0 ± 2.4	11.1 ± 2.5	11.2 ± 2.5	11.6 ± 3.1	0.188
free calcium, Mean ± SD	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.016
urea nitrogen, Mean ± SD	16.4 ± 8.8	15.3 ± 8.0	16.7 ± 8.7	14.7 ± 6.8	18.7 ± 10.8	< 0.001
creatinine, Mean ± SD	1.0 ± 1.0	0.9 ± 0.8	1.0 ± 1.0	0.8 ± 0.5	1.1 ± 1.3	0.064
clinical score						
sofa, Mean ± SD	5.0 ± 2.5	4.9 ± 2.5	5.0 ± 2.1	4.9 ± 2.4	5.2 ± 2.8	0.507
APS III, Mean ± SD	38.6 ± 17.4	36.1 ± 16.8	39.3 ± 18.8	37.4 ± 14.4	41.6 ± 19.0	0.042
outcome						
Two-year mortality, n (%)						0.101
No	552 (93.2)	136 (91.9)	143 (96.6)	140 (94.6)	133 (89.9)	
Yes	40 (6.8)	12 (8.1)	5 (3.4)	8 (5.4)	15 (10.1)	
Three-year mortality, n (%)						0.109

Table 1 (continued)

Variables	Total ($n=592$)	Q1 ($n=148$) [b]	Q2 ($n=148$) [b]	Q3 ($n=148$) [b]	Q4 ($n=148$) [b]	*P* value [a]
No	550 (92.9)	136 (91.9)	142 (95.9)	140 (94.6)	132 (89.2)	
Yes	42 (7.1)	12 (8.1)	6 (4.1)	8 (5.4)	16 (10.8)	
Four-year mortality, n (%)						0.127
No	548 (92.6)	135 (91.2)	142 (95.9)	139 (93.9)	132 (89.2)	
Yes	44 (7.4)	13 (8.8)	6 (4.1)	9 (6.1)	16 (10.8)	
Five-year mortality, n (%)						0.082
No	544 (91.9)	134 (90.5)	141 (95.3)	139 (93.9)	130 (87.8)	
Yes	48 (8.1)	14 (9.5)	7 (4.7)	9 (6.1)	18 (12.2)	

Q1(< 41),Q2(41–57), Q3(41–80) and Q4(> 81)

Abbreviations: % weighted proportion, *BMI* body mass index, *ABPS* Arterial systolic pressure, *ABPD* Arterial diastolic pressure, *COPD* chronic obstructive pulmonary disease, *WBC* white blood cell, *sofa* Sequential Organ Failure Assessment, *APS III* Acute Physiology and Chronic Health Evaluation III

[a] *P* values of multiple comparisons were corrected by the False Discovery Rate method

[b] Q1-Q4: according to Glucose-to-Lymphocyte Ratio (GLR)

p-value ≤ 0.05 was considered statistically significant. The STROBE checklist was followed for reporting.

Results

Baseline characteristics: summarize the socio-demographic and medical characteristics of the cohort, highlighting significant differences across GLR quartiles

Table 1 summarizes the socio-demographic and medical characteristics of the cohort, which included 592 participants with a mean age of 70.0 years and a mean BMI of 30.6. Based on GLR quartiles (Q1: < 41, Q2: 41–57, Q3: 58–80, Q4: > 81), participants were divided into four groups. Significant differences were observed across these groups in age, hypertension prevalence, WBC count, potassium, free calcium, urea nitrogen, and APS III scores. Participants in higher GLR quartiles tended to be older, have higher urea nitrogen levels and APS scores, and have lower rates of hypertension and WBC counts than those in lower GLR quartiles.

Association between GLR and mortality: present the findings of the multiple regression analysis and RCS curves, emphasizing the U-shaped relationship and hazard ratios

In this study, we employed the Cox proportional hazards model primarily due to its suitability for estimating the relationship between event risk and time variation while effectively accommodating multiple covariates. The results of the multiple regression analysis indicated a significant association between the Glucose-to-Lymphocyte Ratio (GLR) and mortality, revealing that both low and high GLR levels were associated with an increased risk of mortality. After adjustment for confounders, the hazard ratios (HRs) for two-year mortality across GLR quartiles Q1, Q3, and Q4 compared with Q2 were 5.62 (95% CI: 1.71–18.48), 1.65 (95% CI: 0.45–5.98), and 3.3 (95% CI: 1.04–10.49), respectively (Table 2). Similar patterns were observed for the three-, four- and five-year outcomes. Additionally, we utilized restricted cubic splines to model the nonlinear relationships between covariates and outcomes, allowing for a more flexible analysis of the data. Restricted cubic spline (RCS) curves showed a U-shaped relationship between GLR and mortality risk in female patients (*P* for nonlinearity < 0.05, Fig. 2), with an inflection point at a GLR of 80. The risk of death was minimized at a GLR of 80; above this threshold, the risk of death increased non-linearly (HR 1.016, 95% CI: 1.003–1.029, $P=0.0186$), whereas below 80, the GLR showed an inverse association with mortality (HR 0.965, 95% CI: 0.937–0.995, $P=0.0221$)(Table 3).

Sensitivity analysis: describe the sensitivity analyses performed and their outcomes, noting any significant interactions or subgroup differences

To assess the robustness of our findings, we conducted several sensitivity analyses under various scenarios. To validate the association between GLR and mortality at one, two, three, four, and five years, stratified analyses were performed based on hypertension, type 2 diabetes, heart failure, myocardial infarction, chronic kidney disease (CKD), acute renal failure, SOFA, and APS. Subgroup analyses showed no significant interactions in the hypertension, type 2 diabetes, heart failure,

Table 2 Multivariable cox regression to assess the association of Glucose-to-Lymphocyte Ratio (GLR) with outcome

	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Two-year mortality										
Continuous variable	1.05 (0.99 ~ 1.12)	0.091	1.05 (0.98 ~ 1.12)	0.158	1.03 (0.96 ~ 1.11)	0.374	1.05 (0.96 ~ 1.14)	0.307	1.05 (0.96 ~ 1.14)	0.302
Categorical variable										
Q1(< 41)	2.47 (0.87 ~ 7.02)	0.089	2.58 (0.9 ~ 7.33)	0.076	3.78 (1.24 ~ 11.47)	0.019	5.55 (1.68 ~ 18.27)	0.005	5.62 (1.71 ~ 18.48)	0.005
Q2(41–57)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3(41–80)	1.62 (0.53 ~ 4.96)	0.396	1.53 (0.5 ~ 4.7)	0.454	1.81 (0.57 ~ 5.75)	0.312	1.67 (0.46 ~ 6.04)	0.438	1.65 (0.45 ~ 5.98)	0.448
Q4(> 81)	3.13 (1.14 ~ 8.6)	0.027	2.92 (1.06 ~ 8.08)	0.039	2.93 (1.03 ~ 8.32)	0.044	3.31 (1.05 ~ 10.41)	0.041	3.3 (1.04 ~ 10.49)	0.043
P for tread		0.376		0.533		0.973		0.779		0.754
Three-year mortality										
Continuous variable	1.06 (1 ~ 1.12)	0.068	1.05 (0.99 ~ 1.12)	0.126	1.04 (0.97 ~ 1.11)	0.285	1.05 (0.97 ~ 1.14)	0.207	1.05 (0.97 ~ 1.15)	0.205
Categorical variable										
Q1(< 41)	2.06 (0.77 ~ 5.5)	0.148	2.18 (0.81 ~ 5.81)	0.121	3.18 (1.11 ~ 9.11)	0.031	4.27 (1.4 ~ 13.03)	0.011	4.44 (1.44 ~ 13.66)	0.009
Q2(41–57)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3(41–80)	1.35 (0.47 ~ 3.9)	0.576	1.28 (0.44 ~ 3.71)	0.645	1.5 (0.5 ~ 4.49)	0.467	1.54 (0.46 ~ 5.11)	0.481	1.53 (0.46 ~ 5.12)	0.486
Q 4(> 81)	2.78 (1.09 ~ 7.11)	0.032	2.62 (1.02 ~ 6.72)	0.045	2.65 (1 ~ 7.03)	0.05	3.01 (1.04 ~ 8.72)	0.042	3.04 (1.03 ~ 8.93)	0.043
P for tread		0.314		0.465		0.885		0.986		0.955
Four-year mortality										
Continuous variable	1.05 (0.99 ~ 1.12)	0.096	1.04 (0.98 ~ 1.11)	0.185	1.04 (0.97 ~ 1.11)	0.301	1.06 (0.97 ~ 1.14)	0.188	1.06 (0.97 ~ 1.15)	0.178
Categorical variable										
Q1(< 41)	2.24 (0.85 ~ 5.88)	0.103	2.38 (0.9 ~ 6.28)	0.08	3.4 (1.21 ~ 9.56)	0.02	4.57 (1.52 ~ 13.71)	0.007	4.74 (1.56 ~ 14.37)	0.006
Q2(41–57)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3(41–80)	1.52 (0.54 ~ 4.28)	0.425	1.43 (0.51 ~ 4.04)	0.496	1.74 (0.6 ~ 5.05)	0.312	1.81 (0.56 ~ 5.81)	0.322	1.85 (0.57 ~ 5.99)	0.305
Q4(> 81)	2.79 (1.09 ~ 7.12)	0.032	2.6 (1.01 ~ 6.68)	0.047	2.73 (1.03 ~ 7.23)	0.043	3.31 (1.14 ~ 9.55)	0.027	3.4 (1.16 ~ 9.96)	0.026
P for tread		0.394		0.598		0.939		0.981		0.98
Five-year mortality										
Continuous variable	1.05 (0.99 ~ 1.11)	0.088	1.04 (0.98 ~ 1.11)	0.174	1.04 (0.97 ~ 1.11)	0.261	1.05 (0.97 ~ 1.13)	0.203	1.05 (0.97 ~ 1.14)	0.193
Categorical variable										
Q1(< 41)	2.07 (0.83 ~ 5.12)	0.117	2.18 (0.88 ~ 5.43)	0.092	2.76 (1.06 ~ 7.2)	0.038	3.61 (1.31 ~ 9.92)	0.013	3.75 (1.35 ~ 10.41)	0.011
Q2(41–57)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3(41–80)	1.31 (0.49 ~ 3.5)	0.597	1.23 (0.46 ~ 3.3)	0.685	1.39 (0.5 ~ 3.83)	0.526	1.36 (0.46 ~ 4.01)	0.579	1.4 (0.47 ~ 4.14)	0.547
Q4(> 81)	2.7 (1.13 ~ 6.45)	0.026	2.51 (1.04 ~ 6.03)	0.04	2.51 (1.02 ~ 6.17)	0.045	2.86 (1.08 ~ 7.52)	0.034	2.93 (1.1 ~ 7.8)	0.032
P for tread		0.341		0.535		0.811		0.962		0.963

Model 1: No adjustment

Model 2: Adjusted for demographic variables (age, BMI)

Model 3: Adjusted for demographic variables, Basic vital signs(ABPS, ABPD, heart rate), comorbidities (Hypertension, diabetes, myocardial infarct, chronic kidney disease, Acute renal failure, stroke, hyperlipidemia, COPD)

Model 4: Adjusted for demographic variables, Basic vital signs, comorbidities, Blood biochemical indicators(WBC, sodium, potassium, calcium total, chloride, anion gap, free calcium, urea nitrogen, creatinine)

Model 5: Adjusted for demographic variables, comorbidities, Basic vital signs, Blood biochemical indicators, SOFA, apsIII

Abbreviations: the change of Glucose-to-Lymphocyte Ratio (GLR) is 10 per, *BMI* body mass index, *ABPS* Arterial systolic pressure, *ABPD* Arterial diastolic pressure, *WBC* white blood cell, *RBC* red blood cell, *RDW* Red blood cell distribution width, *sofa* Sequential Organ Failure Assessment, *APS III* Acute Physiology and Chronic Health Evaluation III, *CRRT* continuous renal replacement therapy, *CI* confidence interval, *HR* hazard ratio, *Ref* reference

myocardial infarction, acute renal failure, SOFA, and APS subgroups (all interaction p-values > 0.05; see Supplementary Figs. 1–4). Notably, GLR was more strongly associated with mortality in patients with CKD (p for interaction < 0.05). Finally, multiple imputation was used to address missing data, and logistic regression on the imputed datasets confirmed result stability (STable 1).

Discussion

This study investigates the potential use of the glucose-lymphocyte ratio (GLR), a blood parameter that combines blood glucose and lymphocyte counts, to assess mortality in female patients undergoing coronary artery bypass grafting (CABG). The results showed a significant U-shaped association between GLR and mortality, with the lowest mortality risk occurring at a GLR of 80.

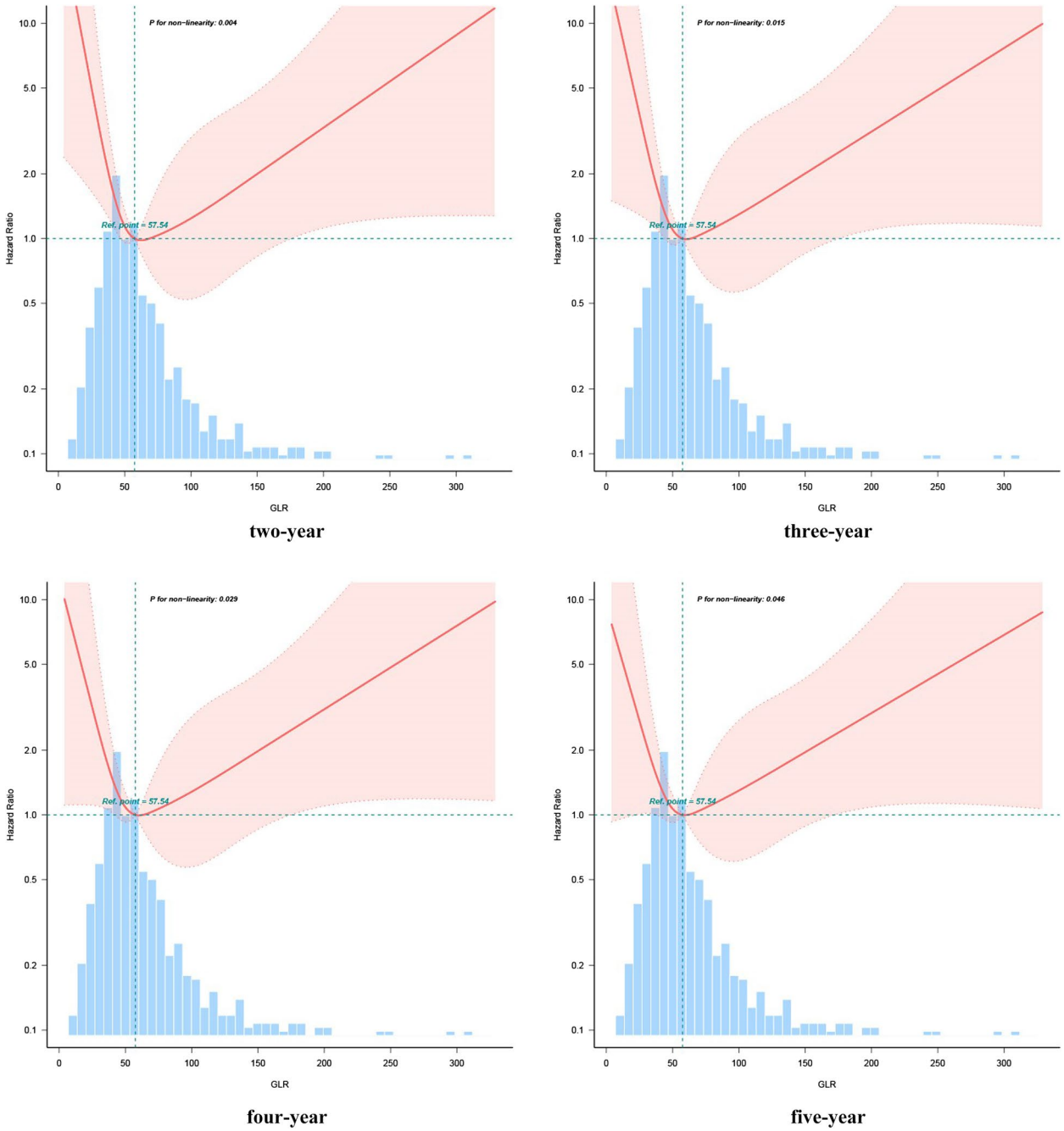

Fig. 2 Dose–response relationships between GLR with mortality rate odds ratio. Solid and dashed lines represent the predicted value and 95% confidence intervals. Adjusted for demographic variables (age, BMI), Basic vital signs(ABPS, ABPD, heart rate), comorbidities (Hypertension, diabetes, myocardial infarct, chronic kidney disease, Acute renal failure, stroke, hyperlipidemia, COPD), Blood biochemical indicators(WBC, sodium, potassium, calcium total, chloride, anion gap, free calcium, urea nitrogen, creatinine) SOFA, apsIII. Abbreviations: BMI: body mass index; ABPS: Arterial systolic pressure; ABPD: Arterial diastolic pressure. COPD: chronic obstructive pulmonary disease, WBC: white blood cell, sofa, Sequential Organ Failure Assessment, APS III: Acute Physiology and Chronic Health Evaluation III; CI: confidence interval; HR: hazard ratio, Ref: reference

Subgroup and sensitivity analyses further validated the robustness of these findings.

As a novel inflammatory marker, the study of the Glucose-to-Lymphocyte Ratio (GLR) in relation to cardiovascular disease has garnered substantial attention. Research involving patients with atherosclerotic cardiovascular disease (ASCVD) demonstrated that elevated GLR is closely linked to an increased risk of both all-cause

Table 3 Threshold effect analysis of relationship of Glucose-to-Lymphocyte Ratio (GLR) with mortality

	mortality rate	
	Adjusted HR (95%CI)	***P* value**
Two model		
GLR ≤ 80	0.965 (0.937,0.995)	0.0221
GLR ≥ 80	1.016 (1.003,1.029)	0.0186
Likelihood Ratio test	-	0.002
Non-linear Test1	-	0.046
Non-linear Test2	-	0.017

Adjusted for demographic variables (age, BMI), Basic vital signs(ABPS, ABPD, heart rate), comorbidities (Hypertension, diabetes, myocardial infarct, chronic kidney disease, Acute renal failure, stroke, hyperlipidemia, COPD), Blood biochemical indicators(WBC, sodium, potassium, calcium total, chloride, anion gap, free calcium, urea nitrogen, creatinine) SOFA, apsIII

Abbreviations: *BMI* body mass index, *ABPS* Arterial systolic pressure, *ABPD* Arterial diastolic pressure, *COPD* chronic obstructive pulmonary disease, *WBC* white blood cell, *sofa* Sequential Organ Failure Assessment, *APS III* Acute Physiology and Chronic Health Evaluation III, *CI* confidence interval, *HR* hazard ratio, *Ref* reference

mortality and cardiovascular disease (CVD) mortality in this population. Notably, the association between GLR and all-cause mortality exhibited a nonlinear pattern [16]. Another study focusing on individuals with acute myocardial infarction (AMI) indicated that, after adjusting for covariates, higher GLR levels were associated with a significantly increased risk of in-hospital mortality [HR = 1.70, 95% CI: (1.24–2.34)]. This suggests that GLR may serve as a potential predictor of AMI prognosis, providing valuable insights for the early identification and management of high-risk populations in clinical settings [15]. Furthermore, stratified analyses revealed that GLR was significantly associated with an elevated risk of CVD mortality among patients who were overweight, had diabetes, or had a history of CVD, corroborating findings from previous studies [14, 21, 22]. However, it is important to note that research regarding coronary artery bypass grafting (CABG) remains limited, particularly in female patients [23] Female sex is recognized as an independent risk factor for adverse cardiac and cerebrovascular events, as well as mortality following CABG [24–26]. Thus, there is an urgent need for further investigation into the determinants of operative outcomes in women, advocating for their consideration as a distinct group in clinical research [5, 10, 11]. To our knowledge, this study is the first to establish an association between GLR and long-term mortality in female CABG patients, underscoring the critical importance of early postoperative management of GLR levels in clinical practice.

An additional significant innovation of this study is the application of restricted cubic spline (RCS) functions to analyze dose–response relationships. Our findings reveal a U-shaped association between the Glucose-to-Lymphocyte Ratio (GLR) and hazard ratios (HRs) for all-cause mortality, indicating that both elevated and diminished levels of GLR are associated with an increased risk of mortality. The Cox proportional hazards model identified a GLR threshold of 80 as the point corresponding to the lowest mortality risk. Specifically, mortality risk decreased as GLR levels increased up to this threshold, while levels exceeding it were associated with an elevated risk. From a clinical practicality perspective, the Glucose-to-Lymphocyte Ratio (GLR) offers distinct advantages over other inflammatory markers, as it can be derived solely from readily available blood parameters. This characteristic enhances its cost-effectiveness, simplicity, and clinical applicability. Additionally, for clinicians observing a sustained elevation in early GLR levels in patients following coronary artery bypass grafting (CABG), this metric may serve as a warning sign and prognostic biomarker, indicating a potential for poor outcomes. Effective management of blood glucose levels and the judicious use of certain antibiotics can influence this indicator. In view of the rising incidence rate of coronary atherosclerotic heart disease, this has certain clinical significance [27, 28].

The mechanism underlying this association is not fully understood, but it is thought to be related to the inflammatory response and metabolic disturbances associated with cardiac surgery. An elevated glucose-to-lymphocyte ratio (GLR) reflects a state of systemic inflammation and metabolic dysregulation, which may contribute to the development of acute kidney injury [17]. In addition, the impaired immune function indicated by a higher GLR may also play a role in the increased risk of postoperative complications [29, 30]. Chronic inflammation is associated with the progression of atherosclerosis and plaque rupture, as highlighted by Yuhua Zhu [31]. Inflammation triggers and accelerates atherosclerotic changes, and we propose that increased inflammatory activation during the perioperative period may significantly affect outcomes. Surgical injury induces endogenous mediators that modify the immune-inflammatory response [32]. Myocardial ischemia/reperfusion injury in the early postoperative phase activates neutrophils, other blood cells, the complement system, and molecular oxygen [33].

This study has several strengths, including its longitudinal design and large sample size. However, several limitations must be acknowledged. First, as a retrospective cohort study, causal inference cannot be made. Although we adjusted for all available confounders, unmeasured confounders may still bias our model. Second, we calculated the glucose-to-lymphocyte ratio (GLR) only after cardiac surgery, without assessing changes during ICU admission. Fourth, over 60% of female patients were

excluded from the study due to missing values for lymphocyte or glucose measurements, which may introduce bias into the results. Future research will aim to address these limitations. Finally, as this study is a single-center retrospective analysis, further validation through prospective multicenter studies is warranted to enhance the generalizability of our findings.

Conclusions

In conclusion, our study identified a U-shaped relationship between the glucose-to-lymphocyte ratio (GLR) and mortality in women undergoing coronary artery bypass grafting (CABG). GLR is a promising, low-cost biomarker. Clinicians should consider monitoring GLR levels in female CABG patients to identify those at higher risk of mortality. Further evidence from larger randomized controlled trials is needed to confirm our results.

Abbreviations

CABG	Coronary artery bypass grafting
GLR	Glucose-to-lymphocyte ratio
MIMIC	Medical Information Mart for Intensive Care
HR	Hazard ratio
CAD	Coronary artery disease
IRB	Institutional Review Board
BMI	Body mass index
ABPS	Arterial systolic pressure
ABPD	Arterial diastolic pressure
COPD	Chronic obstructive pulmonary disease
WBC	White blood cell
SOFA	Sequential Organ Failure Assessment
APS III	Acute Physiology and Chronic Health Evaluation III
MICE	Multivariate Imputation by Chained Equations
IQR	Interquartile ranges
SD	Standard deviation
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
PNI	Prognostic nutritional index
RCS	Restricted cubic spline

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Clinical trial number

Not applicable.

Authors' contributions

KZ contributed as First authors of this manuscript. RZ and MXH were responsible for the concept and design of the study. KZ explain the analysis. BL are responsible for data recovery. BL is the primary corresponding author. All authors critically revised the important intellectual content of the paper and approved the final draft.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. To obtain the application executable files, please contact the author Kai Zhang by email kaizhang@vip.126.com.

Declarations

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), and informed consents were exempted due to all patients' data were anonymized before the data were obtained. We also complied with all relevant ethical regulations regarding the use of the data in our study. All reports adhered to the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology and the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

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