Relationship between the Glucose to Lymphocyte Ratio and 30-day mortality in acute myocardial infarction patients: An analysis from the MIMIC-IV Database

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Research Article

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Abstract

Aim：To investigate the association between the glucose to lymphocyte ratio (GLR) and 30-day mortality in acute myocardial infarction (AMI) patients.

Methods：A retrospective cohort analysis. Two thousand nine hundred and eleven AMI patients were enrolled using the Medical Information Mart for Intensive Care (MIMIC)-IV database. The patients were divided into four groups according to their GLR quantiles. The primary outcome was 30-day mortality. Multivariate Cox proportional risk regression models were used to examine the association between GLR and 30-day mortality. The non-linear relationship between GLR and 30-day mortality was confirmed using a Cox proportional risk regression model fitted by cubic spline function and smooth curve fitting.

Results：Of the 2,911 participants, 426 (14.63%) died. The generalized additive model (GAM) showed that the relationship between admission GLR levels and 30-day mortality among AMI patients was non-linear (hazard ratio [HR] 1.01, 95% confidence interval [CI] 1.00–1.02, p = 0.0134). In addition,adjusted multivariable Cox regression analysis confirmed that the admission GLR levels of 3.60-6.06 was independently associated with decreased mortality compared to GLR levels of 0.60–3.59 (HR 1.49, 95% CI 1.02–2.18, p = 0.0409), GLR levels of 6.07–11.03 (HR 1.56, 95% CI 1.07–2.26, p = 0.0203), and GLR levels of 11.04-97.55 (HR 1.69, 95% CI 1.17–2.42, p = 0.0047). A two-piecewise regression model was used to obtain a threshold inflection point value of 4.66. The HR and the 95% CI on the left inflection point were 1.33 and 1.07–1.65, respectively, (p = 0.0116); on the right inflection point, they were 1.01 and 1.01–1.02, respectively, (p = 0.2630).

Conclusions：The relationship between the GLR and 30-day mortality was nonlinear in AMI patients. The GLR was positively related with 30-day mortality when the GLR was less than 4.66.

Introduction

Acute myocardial infarction (AMI) is a leading cause of mortality worldwide, and 30-day mortality for patients with cardiogenic shock due to myocardial infarction is approximately 40% [1, 2]. AMI is caused by acute obstruction of the coronary arteries, leading to acute, persistent ischemia and hypoxia and eventually resulting in myocardial necrosis [3, 4]. Therefore, validating biomarkers with the predictive value of long-term mortality in AMI patients has become increasingly important for identifying high-risk individuals. In a previous MIMIC-III database study found that higher estimated plasma volume status (EPVS) values is a predictor for predicting in-hospital mortality of AMI [5].In recent years, a series of studies on the GLR and prognosis of cancer patients have been reported [6–10], few studies on the GLR and prognosis of acute kidney injury after cardiac surgery and acute respiratory distress syndrome in patients in the intensive care unit(ICU)have been reported [11–12]. However, there are currently no relevant studies reporting the effect of GLR on the prognosis of AMI patients and the correlation of adverse events. To the best of our knowledge, this is one of the first studies using the MIMIC-IV database to research the results of AMI. Using the US MIMIC-IV database (version 1.0) [13], we evaluated AMI's severity and prognosis as a large sample retrospective analysis.

Materials And Methods

2.1. Data Source

The patients were identifed in the MIMIC-IV database from 2008 to 2019. This database was identified according to the Health Insurance Portability and Accountability Act Safe Harbor provision and has approval from the Massachusetts Institute of Technology and the Institutional Review Board of Beth Israel Deaconess Medical Center (BIDMC)[14]. The authors, Zuoan Qin, completed the Collaborative Institutional Training Initiative examination (certification number: 36208651) to access the database for the data extraction.

2.2. Study Population and Variable Extraction

A total of 13,015 patients admitted to the ICU and diagnosed with an AMI were considered for this research. The inclusion criterion was AMI, defined as ICD-9 codes of 410.00–410.92 or ICD-10 codes of I21. Exclusion criteria included: (1) patients with repeated admissions (n=6475); (2) less than 24 hours of ICU stay (n=883); (3) either glucose or lymphocyte values missing at admission (n=2116);(4) patients with incomplete data, more than 10% of values missing (n=58). Finally, 2911 patients were included in the study, and these patients were followed up for at least 30 days after admission.All experiments were performed following The First People's Hospital of Changde City and national guidelines and regulations, and the experiment was approved by the ethics committee of The First People's Hospital of Changde City（2022-050-01）.

2.3. Definition of GLR and the Outcome Measurement

The GLR is defined using the following equation: GLR = Glucose (mmol/L)/Lymphocyte (10^9/L)[10]. The primary outcome was set to 30-days mortality patients discharged from the hospital alive before 30 days were considered alive at Day 30. The variables in this study included patient characteristics, comorbidities, laboratory variables, a severity scoring system, drug use, treatment information, ICU length of stay (ICU LOS) (days) and time of death. The patient variables were collected as follows:(1) Characteristics: age, gender, heart rate (beats/minute), mean blood pressure (MBP) (mmHg), respiratory rate (breath/minute), temperature (C), peripheral oxygen saturation (SpO2) (%);(2) Comorbidities: hypertension, hyperlipidemia, diabetes, congestive heart failure, atrial fibrillation (AF), peripheral vascular disease, cerebrovascular disease, renal disease, severe liver disease, cancer;(3) The first value of vital signs and laboratory data within 24 h of ICU admission laboratory parameters: white blood cell (WBC), red blood cell, hemoglobin, platelets, lymphocytes, monocytes, neutrophils, creatinine, blood urea nitrogen (BUN), anion gap, glucose; (4) Severity scoring system: sequential organ failure assessment (SOFA) score, simplified acute physiology score (SAPS) II, (5)Drug use: aspirin, clopidogrel, ticagrelor, dobutamine,dopamine,epinephrine,beta-blockers;(6)Treatment information: percutaneous transluminal coronary angioplasty, percutaneous coronary intervention, coronary artery bypass grafting (CABG);(7) ICU LOS (days) and 30-day mortality.

2.4. Statistical analysis

In the first step, we listed the participants' baseline data (Table 1). The continuous variables were expressed as mean ± standard deviation (SD). The classification variables were expressed as frequency and percentage. In the second step, a one-way analysis of variance test (normal distribution) or a Kruskal–Wallis H test (skew distribution) was used to detect the difference between the different GLR (four quantiles). Univariate and multivariate Cox proportional hazard regression models were used to build three different models, including a crude model (unadjusted for covariates), model 1 (adjusted for age and gender only) and model 2 (adjusted for potential confounding factors). Weighted univariate and multivariate Cox were applied based on the recommendations of the STROBE statement. Similarly, the results of unadjusted, minimum adjusted, and fully adjusted analyses were demonstrated. The following principle determined whether to adjust the covariance or not: when added to the model, the matching odds ratio was changed by at least 10%. In addition, the GAM was used to identify the non-linear relationships. If a non-linear correlation was observed, a two-piece linear regression model was performed to calculate the threshold effect of the GLR on 30-day mortality based on the smoothed graph. When the ratio of the GLR to the 30-day mortality was obvious in the smooth curve, the recursive method automatically calculated the inflection point, and the maximum model likelihood was used. Data analysis was performed using the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3) and Empower Stats (www. empowerstats.com; X&Y Solutions, Inc.).

Results

3.1. Selection of participants

The study assessed 5,968 patients admitted to the ICU due to an AMI, of which 3,057 were excluded. Of the 3,057 patients excluded, 883 had less than 24 hours of ICU stay, 2,116 were without glucose or lymphocyte data and 58 with incomplete data had more than 10% of values missing. A total of 2,911 participants were selected for the final data analysis (see the flowchart in Figure 1).

3.2. Baseline characteristics

The mean age of the participants was 71.26 ± 13.11 years, 1850 (63.55%) were females, and 426 (14.63%) died within 30 days. According to the GLR values, 727, 728, 728, and 728 patients belonged to the Q1 (≥ 0.60 and < 3.59), Q2 (≥ 3.60 and < 6.06), Q3 (≥ 6.07 and < 11.03), and Q4 (≥ 11.04 and < 97.55) categories, respectively. The different groups were evaluated by the Pearson $\chi 2$ test for the binary variables and the t-test for the continuous variables. The continuous variables were expressed as mean ± SD, and the binary variables were expressed as counts and proportions. All variables are listed in Table 1.

3.3. Univariate analysis

Table 2. shows the results of the univariate analysis indicating GLR (p < 0.0001), age (p < 0.0001), heart rate (p = 0.0003) Respiratory rate (p < 0.0001) WBC (p = 0.0001), monocytes (p = 0.0498), neutrophils (p < 0.0001) creatinine (p =0.0173) BUN (p < 0.0001), anion gap (p < 0.0001), glucose (p < 0.0001), atrial fibrillation (p =0.0471) severe liver disease (p =0.0006) dobutamine use (p < 0.0001), dopamine use (p < 0.0001), epinephrine use (p < 0.0001), SOFA (p < 0.0001), SAPSII (p < 0.0001) positively correlated with mortality, Temperature (p =0.0041), SpO2 (p < 0.0001), bicarbonate (p < 0.0001), hypertension (p =0.0004), hyperlipidemia (p < 0.0001), aspirin use (p < 0.0001), clopidogrel use (p < 0.0167), beta blockers use (p < 0.0001), CABG (p < 0.0001) negatively correlated with mortality.

3.4. The Association Between the GLR and 30-day Mortality

We used a univariate and multivariate Cox proportional-hazards regression models were introduced to evaluate the associations between the GLR and 30-day mortality in AMI patients. Meanwhile, the non-adjusted and adjusted models are shown in Table 3. We found that lower GLR was associated with increased risk of 30-day mortality (non-adjusted model: HR 1.02, 95% CI 1.01-1.02, p <0.0001; minimally-adjusted model: HR 1.02, 95% CI 1.01-1.02, p <0.0001; fully-adjusted model: HR 1.01, 95% CI 1.00-1.02, p = 0.0134). The GLR was also treated as a categorical variable (the four quantiles) for sensitivity analysis, and the same trend was observed.

3.5 Analysis of the non-linear relationship between the GLR and 30-day mortality

This study observed that the relationship between the GLR and 30-day mortality in patients with an AMI was non-linear (Figure 2) after adjusting for gender, age, hypertension, hyperlipidemia, atrial fibrillation, peripheral vascular diseases, cerebrovascular disease, renal disease, cancer, severe liver disease, heart rate, respiratory rate, temperature, SpO2, anion gap, BUN, bicarbonate, creatinine, monocytes, neutrophils, platelet, WBC, aspirin, clopidogrel, dobutamine, dopamine, epinephrine, beta-blockers. The inflection point of 4.66 (GLR = 4.66) was obtained using a two-segment linear regression model (Table 4). There was no significant correlation to the right of the inflection point (HR 1.01, 95% CI 1.00–1.02, p = 0.2630); however, there was a positive correlation between the GLR value and all-cause mortality to the left of the threshold inflection point (HR 1.33, 95% CI 1.07–1.65, p = 0.0116).

Discussion

In this retrospective study of 2,911 patients with AMI in ICU, the potential non-linear trend between the GLR and 30-day mortality in AMI patients was revealed. This large retrospective cohort study of critically ill patients with an AMI has demonstrated that patients with a high GLR are more likely to have a higher risk of 30-day mortality even after adjusting for traditional cardiovascular risk factors.

In the past few decades, mortality from cardiovascular disease has been reduced partly because of the improved management of AMI [15]. However, AMI is the most serious manifestation of coronary heart disease and the main cause of global cardiovascular diseases morbidity and mortality [1,2]. Therefore, all patients with AMI should undergo an early assessment of short-term risk; though the Global Registry of Acute Coronary Events (GRACE) risk score has been developed [16], it is relatively complex. Based on previous studies investigating the prognostic value of glucose levels and lymphocyte counts in AMI patients, we report for the first time that the first GLR level within 24 hours of admission can be used as a preliminary prognostic indicator of short-term mortality. Many studies have shown a relationship between high blood glucose levels on admission and an increased risk of mortality and poor outcomes after AMI [17-19]. This relationship is accounted for by diabetes being one of the main risk factors for coronary atherosclerosis, which increases the probability of myocardial infarction. Additionally, patients with AMI often have stress hyperglycemia. The mean blood glucose of the participants was 9.26 ± 4.69 mmol/L, and univariate analysis found that blood glucose was associated with 30-day mortality (HR 1.04, 95% CI 1.02–1.06, p < 0.0001). Lymphocytes represent a quiescent and control inflammatory pathway in suppressed immune response [20]. They play a role in processes involved in plaque growth, lipid core development, myocardial infarction and heart failure [21,22]. Lymphocytopenia has been detected in critical inflammatory states and is associated with cardiovascular diseases [23]. A low blood lymphocyte count has been shown to be related to worse cardiovascular consequences in patients with AMI [24–26]. Thus, the combination of increased glucose and low levels of lymphocytes may provide more information than either glucose level or lymphocyte count alone. Recent studies have found that GLR is associated with a poor prognosis of cancer, acute respiratory distress syndrome and acute kidney injury after cardiac surgery [6-12]. We believe that the GLR can be used to predict the prognosis of AMI patients because its value reflects the activity of inflammatory and thrombotic processes.

In this study, the univariate analysis showed that blood lymphocyte count was associated with 30-day mortality (HR 0.93, 95% CI 0.84–1.02, p= 0.1160). Similarly, the univariate analysis found that GLR was associated with 30-day mortality (HR 1.02, 95% CI 1.01–1.02, p<0.0001). Our study is consistent with the previous finding, but we further expounded on the existing knowledge. The relationship between 30-day mortality in AMI patients and the GLR values was non-linear; low-level GLR values increased the risk of death in AMI patients.

Our study had several strengths. (1) Our study was the first undertaken to research the mortality risk factors of AMI patients. This study focused on the compound variables of the GLR and was the first to investigate the relationship between the GLR and mortality in AMI patients. (2) The study used real-world data for a large and diverse population study design. (3) We used a two-part Cox proportional risk regression model to perform a threshold effect analysis on the relationship between the GLR and 30-day mortality. (4) We analyzed the

exposure variable, GLR, as continuous and categorical variables and calculated the HR using binary logistic regression models. Such a method can minimize the incidence of a contingency in the statistical analysis and enhance the reliability of the final results.

Our study also had a few limitations. (1) This was a single-center retrospective observational study, so it was difficult to avoid selection bias. (2) Although we adjusted for certain factors, other unknown factors may have influenced our results. (3) No long-term follow-up events were provided from the MIMIC-IV database.

Conclusions

The relationship between the GLR and 30-day mortality was nonlinear in AMI patients. The GLR was positively related with 30-day mortality when the GLR was less than 4.66.

Abbreviations

GLR：glucose to lymphocyte ratio;AMI:acute myocardial infarction;MIMIC:Medical Information Mart for Intensive Care;GAM:generalized additive model;HR:hazard ratio;CI:confidence interval;EPVS:estimated plasma volume status;ICU:intensive care unit;BIDMC:Beth Israel Deaconess Medical Center;BUN: blood urea nitrogen; MBP:Mean Blood Pressure; SpO2: saturation of peripheral oxygen; WBC: white blood cell；RBC: red blood cell；SAPSII: simplified acute physiology score II; SOFA: sequential organ failure assessment score; MBP:mean blood pressure; PTCA:percutaneous transluminal coronary angioplasty;PCI:percutaneous coronary intervention; CABG:coronary artery bypass grafting; ICU LOS: Intensive care unit length of stay.

Declarations

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Authors' contributions

Conceptualization: Z-A.Q. and L.L.; methodology: Z-A.Q. and Q.Z.; software: Z-A.Q., X-J.D. and Q.Z.; validation: L.L.; formal analysis: Z-A.Q.; investigation: Z-A.Q.; resources: Z-A.Q.; data curation: Z-A.Q., Q.Z. and X-J.D.; writing—original draft preparation: L.L.and Z-A.Q.; writing—review and editing: L-Q.G. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets analysed during the current study are available in the MIMIC-IV repository, https://mimic.mit.edu/docs/iv/

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests related to this work.

Availability of data and materials

The MIMIC-IV database was built by the Massachusetts Institute of Technology and was approved to waive the documentation of informed consent by the Institutional Review Board of Beth Israel Deaconess Medical Center. For the access of the database, Zuoan Qin completed the Collaborative Institutional Training Initiative course named “Data or Specimens Only Research” and obtained the relevant certification (certification number:36208651).

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References

1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of AMI in patients presenting with ST-segment elevation: The Task Force for

the management of AMI in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-177.

2. Marc D Samsky , David A Morrow , Alastair G Proudfoot , Judith S Hochman , Holger Thiele , Sunil V Rao . Cardiogenic Shock After Acute Myocardial Infarction: A Review.JAMA. 2021 Nov 9;326(18):1840-1850.doi: 10.1001/jama.2021.18323.

3. Piamsiri C, Maneechote C, Siri-Angkul N, Chattipakorn SC, Chattipakorn N. Targeting necroptosis as therapeutic potential in chronic myocardial

infarction. J Biomed Sci. 2021;28(1):25. doi:10.1186/s12929-021-00722-w

4. Tang Y, Chen Q, Zha L, et al. Development and Validation of Nomogram to Predict Long-Term Prognosis of Critically Ill Patients with Acute Myocardial Infarction. Int J Gen Med. 2021;14:4247–4257. doi:10.2147/IJGM.S310740

5.Jun Chen , Jiayi Shen , Dongsheng Cai , Tiemin Wei , Renyi Qian , Chunlai Zeng,et al.Estimated plasma volume status (ePVS) is a predictor for acute myocardial infarction in-hospital mortality: analysis based on MIMIC-III database.BMC Cardiovasc Disord. 2021 Nov 8;21(1):530.doi: 10.1186/s12872-021-02338-2.

6.Yongjun Chen , Shangjun Tang , Yumei Wang.Prognostic Value of Glucose-to-Lymphocyte Ratio in Critically Ill Patients with Acute Pancreatitis.Int J Gen Med. 2021 Sep 8;14:5449-5460. doi: 10.2147/IJGM.S327123.

7.Ali Yılmaz , Melih Şimşek , Zekeriya Hannarici , Mehmet E Büyükbayram , Mehmet Bilici , Salim B Tekin .The importance of the glucose-to-lymphocyte ratio in patients with hepatocellular carcinoma treated with sorafenib.Future Oncol. 2021 Nov;17(33):4545-4559. doi: 10.2217/fon-2021-0457.

8.Yueming Zhang , Yaolin Xu , Dansong Wang , Tiantao Kuang , Wenchuan Wu , Xuefeng Xu.Prognostic value of preoperative glucose to lymphocyte ratio in patients with resected pancreatic cancer.Int J Clin Oncol. 2021 Jan;26(1):135-144. doi: 10.1007/s10147-020-01782-y.

9.Ailing Zhong , Chien-Shan Cheng , Jinyan Kai , Renquan Lu , Lin Guo.Clinical Significance of Glucose to Lymphocyte Ratio (GLR) as a Prognostic Marker for Patients With Pancreatic Cancer.Front Oncol. 2020 Sep 30;10:520330.doi: 10.3389/fonc.2020.520330.

10.Jonathan Navarro , Incheon Kang , Ho Kyoung Hwang , Dong Sup Yoon , Woo Jung Lee , Chang Moo Kang.Glucose to Lymphocyte Ratio as a Prognostic Marker in Patients With Resected pT2 Gallbladder Cancer.J Surg Res. 2019 Aug;240:17-29. doi: 10.1016/j.jss.2019.02.043.

11.Lu Li , Gaorui Zou , Jie Liu .Preoperative Glucose-to-Lymphocyte Ratio is an Independent Predictor for Acute Kidney Injury After Cardiac Surgery in Patients in Intensive Care Unit.Int J Gen Med. 2021 Oct 8;14:6529-6537. doi: 10.2147/IJGM.S335896.

12.Yi Zhang , Shuo Zhang .Prognostic value of glucose-to-lymphocyte ratio in critically ill patients with acute respiratory distress syndrome: A retrospective cohort study.J Clin Lab Anal. 2022 Mar 31;e24397. doi: 10.1002/jcla.24397.

13.A L Goldberger , L A Amaral, L Glass, et al.PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals.Circulation. 2000 Jun 13;101(23):E215-220.

14.Alistair Ew Johnson , David J Stone , Leo A Celi , Tom J Pollard .The MIMIC Code Repository: enabling reproducibility in critical care research.J Am Med Inform Assoc. 2018 Jan 1;25(1):32-39.

15. Salim S Virani, Alvaro Alonso, Emelia J Benjamin, Marcio S Bittencourt, Clifton W Callaway, April P Carson,et al.Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association.Circulation. 2020 Mar 3;141(9):e139-e596.doi: 10.1161/CIR.0000000000000757.

16.Keith A A Fox , Omar H Dabbous, Robert J Goldberg, Karen S Pieper, Kim A Eagle, Frans Van de Werf, et al.Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE).BMJ. 2006 Nov 25;333(7578):1091. doi: 10.1136/bmj.38985.646481.55.

17. Keiichi Tsuchida , Norihito Nakamura , Satoshi Soda , Ryohei Sakai , Kota Nishida , Jiro Hiroki , et al. Relationship between glucose fluctuations and ST-segment resolution in patients with ST-elevation acute myocardial infarction. Int Heart J. 2017 May 31;58(3):328-334.doi: 10.1536/ihj.16-250.

18.Fang-Hong Shi , Long Shen , Jiang Yue , Jing Ma , Zhi-Chun Gu , Hao Li .et al.Intervention by clinical pharmacists can improve blood glucose fluctuation in patients with diabetes and acute myocardial infarction: A propensity score-matched analysis.Pharmacol Res Perspect. 2021 Apr;9(2):e00725.

doi: 10.1002/prp2.725.

19.Ramin Eskandari , Parisa Matini , Sepideh Emami , Yousef Rezaei.Association between admission blood glucose and prognosis in non-diabetic patients with first-ever acute myocardial infarction.Rom J Intern Med. 2022 Mar 17;60(1):34-41.

doi: 10.2478/rjim-2021-0033.

20.Alparslan Kurtul , Mikail Yarlioglues , Sani Namik Murat , Gokhan Ergun , Mustafa Duran , Haci Ahmet Kasapkara ,et al.Usefulness of the platelet-to-lymphocyte ratio in predicting angiographic reflow after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction.Am J Cardiol. 2014 Aug 1;114(3):342-7. doi: 10.1016/j.amjcard.2014.04.045.

21.Yanyi Sun , Cristina Pinto , Stéphane Camus , Vincent Duval , Paul Alayrac , Ivana Zlatanova ,et al.Splenic Marginal Zone B Lymphocytes Regulate Cardiac Remodeling After Acute Myocardial Infarction in Mice.J Am Coll Cardiol. 2022 Feb 22;79(7):

632-647.doi: 10.1016/j.jacc.2021.11.051.

22.Yasmine Zouggari , Hafid Ait-Oufella, Philippe Bonnin, Tabassome Simon, Andrew P Sage, Coralie Guérin,et al.B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction.Nat Med. 2013 Oct;19(10):1273-80. doi: 10.1038/nm.3284.

23.J Núñez , G Miñana, V Bodí, E Núñez, J Sanchis, O Husser, A Llàcer.Low lymphocyte count and cardiovascular diseases.Curr Med Chem.

2011;18(21):3226-33.doi: 10.2174/092986711796391633.

24.Luke Spray , Catherine Park , Suzanne Cormack , Ashfaq Mohammed , Pedram Panahi , Stephen Boag,et al.The Fractalkine Receptor CX 3 CR1 Links Lymphocyte Kinetics in CMV-Seropositive Patients and Acute Myocardial Infarction With Adverse Left Ventricular Remodeling.Front Immunol. 2021 May 5;12:605857.doi: 10.3389/fimmu.2021.605857.

25.Bryan Richard Sasmita , Yuansong Zhu , Hongbo Gan , Xiankang Hu , Yuzhou Xue , Zhenxian Xiang,et al.Prognostic value of neutrophil-lymphocyte ratio in cardiogenic shock complicating acute myocardial infarction: A cohort study.Int J Clin Pract 2021 Oct;75(10):e14655.doi: 10.1111/ijcp.14655.

26.Tang-Meng Guo , Bei Cheng , Li Ke , Si-Ming Guan , Ben-Ling Qi , Wen-Zhu Li , Bin Yang, et al.Prognostic Value of Neutrophil to Lymphocyte Ratio for In-hospital Mortality in Elderly Patients with Acute Myocardial Infarction.Curr Med Sci.2018 Apr;38(2):354-359.doi: 10.1007/s11596-018-1887-0.

Tables

Table1. Baseline characteristics

	GLR				
	Q1(0.60-3.59) (n=727)	Q2(3.60-6.06) (n=728)	Q3(6.07-11.03) (n=728)	Q4(11.04-97.55) (n=728)	*P*-value
GLR	2.56 ± 0.70	4.74 ± 0.70	8.26 ± 1.43	22.37 ± 13.41	<0.001
Characteristic					
Age, （year）	77.86 ± 11.14	78.74 ± 10.89	78.95 ± 10.66	74.53 ± 12.26	<0.001
Gender, n (%)					0.036
Female	493 (67.81%)	451 (61.95%)	444 (60.99%)	462 (63.46%)	
Male	234 (32.19%)	277 (38.05%)	284 (39.01%)	266 (36.54%)	
Heart rate (beats/minute)	83.09 ± 16.15	85.57 ± 17.12	88.25 ± 19.43	90.99 ± 20.26	<0.001
Respiratory rate (breath/minute)	17.58 ± 5.39	18.65 ± 5.92	20.08 ± 6.10	20.99 ± 6.10	<0.001
MBP (mmHg)	81.15 ± 15.82	82.85 ± 17.16	83.81 ± 19.33	83.76 ± 19.26	0.015
Temperature (∘ C)	36.50 ± 0.66	36.60 ± 0.68	36.64 ± 0.82	36.64 ± 0.98	0.003
SPO2 (%)	97.95 ± 3.05	97.16 ± 4.69	96.44 ± 4.72	96.15 ± 4.30	<0.001
Comorbidities,*n* (%)					
Hypertension	335 (46.08%)	352 (48.35%)	289 (39.70%)	252 (34.62%)	<0.001
Hyperlipidemia	438 (60.25%)	434 (59.62%)	403 (55.36%)	388 (53.30%)	0.018
Diabetes	188 (25.86%)	195 (26.79%)	221 (30.36%)	274 (37.64%)	<0.001
Atrial fibrillation	218 (29.99%)	257 (35.30%)	270 (37.09%)	282 (38.74%)	0.003
Congestive heart failure	268 (36.86%)	353 (48.49%)	434 (59.62%)	465 (63.87%)	<0.001
Peripheral vasculard	103 (14.17%)	93 (12.77%)	124 (17.03%)	122 (16.76%)	0.066
Cerebro vascular disea	92 (12.65%)	91 (12.50%)	113 (15.52%)	102 (14.01%)	0.300
Rennal disease	173 (23.80%)	169 (23.21%)	247 (33.93%)	282 (38.74%)	<0.001
Severe liver disease	6 (0.83%)	6 (0.82%)	12 (1.65%)	26 (3.57%)	<0.001
Malignant cancer	39 (5.36%)	50 (6.87%)	51 (7.01%)	85 (11.68%)	<0.001
Laboratory parameters					
WBC (10^9/L)	14.08 ± 9.75	12.50 ± 5.99	12.93 ± 6.13	13.31 ± 7.36	<0.001
RBC (10^{12}/L)	3.71 ± 0.87	3.75 ± 0.92	3.74 ± 0.86	3.74 ± 0.84	0.834
Hemoglobin (g/L)	11.04 ± 2.60	11.22 ± 2.72	11.20 ± 2.57	11.20 ± 2.45	0.521
Platelet (10^9/L)	214.43 ± 101.16	222.94 ± 103.86	226.87 ± 109.16	212.43 ± 104.07	0.025
Lymphocytes (10^9/L)	2.84 ± 1.40	1.71 ± 0.66	1.19 ± 0.50	0.69 ± 0.40	<0.001
Monocytes (10^9/L)	0.74 ± 0.86	0.66 ± 0.48	0.70 ± 0.48	0.63 ± 0.48	0.002
Neutrophils (10^9/L)	10.65 ± 5.90	10.10 ± 5.42	11.04 ± 5.62	11.78 ± 6.91	<0.001
Creatinine (mEq/L)	1.38 ± 1.44	1.55 ± 2.06	1.82 ± 1.71	2.10 ± 2.01	<0.001
BUN (mg/dL)	24.65 ± 19.48	27.33 ± 20.56	34.49 ± 27.07	39.61 ± 27.89	<0.001
Anion gap（mmol/L）	14.47 ± 4.44	15.66 ± 4.70	16.95 ± 4.95	18.39 ± 4.96	<0.001
Bicarbonate (mmol/L)	22.94 ± 3.89	22.67 ± 4.38	21.78 ± 4.76	20.66 ± 4.97	<0.001
Glucose (mmol/L)	6.68 ± 2.17	7.93 ± 2.88	9.64 ± 3.85	12.80 ± 6.25	<0.001
Drugs use,*n* (%)					
Aspirin	684 (94.09%)	659 (90.52%)	658 (90.38%)	626 (85.99%)	<0.001
Clopidogrel	208 (28.61%)	274 (37.64%)	307 (42.17%)	302 (41.48%)	<0.001
Ticagrelor	49 (6.74%)	60 (8.24%)	59 (8.10%)	38 (5.22%)	0.085
Dobutamine	11 (1.51%)	33 (4.53%)	44 (6.04%)	52 (7.14%)	<0.001
Dopamine	14 (1.93%)	57 (7.83%)	68 (9.34%)	90 (12.36%)	<0.001
Epinephrine	121 (16.64%)	84 (11.54%)	68 (9.34%)	61 (8.38%)	<0.001
Beta blockers	452 (62.17%)	423 (58.10%)	449 (61.68%)	378 (51.92%)	<0.001
Scoring systems					
SAPSII	36.84 ± 13.52	38.27 ± 13.92	40.72 ± 14.05	43.48 ± 13.88	<0.001
SOFA	5.24 ± 3.45	5.49 ± 3.77	6.15 ± 4.08	7.44 ± 4.24	<0.001
Treatment information,*n* (%)					
PTCA	1 (0.14%)	8 (1.10%)	15 (2.06%)	4 (0.55%)	0.001
PCI	118 (16.23%)	150 (20.60%)	153 (21.02%)	131 (17.99%)	0.064
CABG	276 (37.96%)	153 (21.02%)	75 (10.30%)	16 (2.20%)	<0.001
ICU LOS (days)	3.15 ± 3.81	3.86 ± 4.17	4.56 ± 5.30	5.62 ± 6.68	<0.001
Die within 30 days ,n (%)	43 (5.91%)	89 (12.23%)	116 (15.93%)	178 (24.45%)	<0.001

Exposure: GLR:Glucose-to-Lymphocyte Ratio;BUN: blood urea nitrogen; MBP:Mean Blood Pressure; SpO2: saturation of peripheral oxygen; WBC: white blood cell；RBC: red blood cell；SAPSII: simplified acute physiology score II; SOFA: sequential organ failure assessment score; MBP:mean blood pressure; PTCA:percutaneous transluminal coronary angioplasty;PCI:percutaneous coronary intervention; CABG: coronary artery bypass grafting; ICU LOS: Intensive care unit length of stay.

Table 2.Factors correlated to 30-day mortality in GLR by Univariate Analysis.

Death	Statistics	HR(95%CI), *P*- value
GLR	9.49 ± 10.26	1.02 (1.01, 1.02) <0.0001
Age, （year）	71.26 ± 13.11	1.02 (1.01, 1.03) <0.0001
Gender, n (%)		
Female	1850 (63.55%)	1.0
Male	1061 (36.45%)	1.24 (1.02, 1.50) 0.0312
Heart rate (beats/minute)	86.97 ± 18.54	1.01 (1.00, 1.01) 0.0003
Respiratory rate (breath/minute)	19.32 ± 6.03	1.06 (1.05, 1.07) <0.0001
MBP (mmHg)	82.89 ± 17.98	1.00 (0.99, 1.00) 0.4377
Temperature (∘ C)	36.59 ± 0.80	0.86 (0.78, 0.95) 0.0041
SPO2 (%)	96.93 ± 4.30	0.97 (0.96, 0.98) <0.0001
WBC (10^9/L)	13.20 ± 7.48	1.01 (1.01, 1.02) 0.0001
RBC (10^{12}/L)	3.73 ± 0.87	1.04 (0.93, 1.16) 0.5010
Hemoglobin (g/L)	11.17 ± 2.59	1.00 (0.96, 1.04) 0.9554
Platelet (10^9/L)	219.17 ± 104.72	1.00 (1.00, 1.00) 0.9526
Lymphocytes (10^9/L)	1.61 ± 1.16	0.93 (0.84, 1.02) 0.1160
Monocytes (10^9/L)	0.68 ± 0.60	1.09 (1.00, 1.18) 0.0498
Neutrophils (10^9/L)	10.89 ± 6.02	1.03 (1.02, 1.05) <0.0001
Creatinine (mEq/L)	1.71 ± 1.84	1.04 (1.01, 1.07) 0.0173
BUN (mg/dL)	31.52 ± 24.75	1.01 (1.01, 1.01) <0.0001
Anion gap（mmol/L）	16.37 ± 4.99	1.09 (1.07, 1.10) <0.0001
Bicarbonate (mmol/L)	22.01 ± 4.61	0.94 (0.92, 0.95) <0.0001
Glucose (mmol/L)	9.26 ± 4.69	1.04 (1.02, 1.06) <0.0001
Hypertension		
no	1683 (57.82%)	1.0
yes	1228 (42.18%)	0.69 (0.56, 0.85) 0.0004
Hyperlipidemia		
no	1248 (42.87%)	1.0
yes	1663 (57.13%)	0.62 (0.52, 0.76) <0.0001
Diabetes		
no	2033 (69.84%)	1.0
yes	878 (30.16%)	1.12 (0.92, 1.37) 0.2680
Atrial fibrillation		
no	1884 (64.72%)	1.0
yes	1027 (35.28%)	1.21 (1.00, 1.47) 0.0471
Congestive heart failure		
no	1391 (47.78%)	1.0
yes	1520 (52.22%)	1.07 (0.88, 1.30) 0.4917
Peripheral vasculard		

no	2469 (84.82%)	1.0
yes	442 (15.18%)	1.01 (0.78, 1.30) 0.9619
Cerebro vascular disea		
no	2513 (86.33%)	1.0
yes	398 (13.67%)	1.11 (0.86, 1.41) 0.4252
Rennal disease		
no	2040 (70.08%)	1.0
yes	871 (29.92%)	1.16 (0.95, 1.41) 0.1336
Severe liver disease		
no	2861 (98.28%)	1.0
yes	50 (1.72%)	2.19 (1.40, 3.43) 0.0006
Malignant cancer		
no	2686 (92.27%)	1.0
yes	225 (7.73%)	1.31 (0.98, 1.75) 0.0638
Aspirin		
no	284 (9.76%)	1.0
yes	2627 (90.24%)	0.39 (0.31, 0.49) <0.0001
Clopidogrel		
no	1820 (62.52%)	1.0
yes	1091 (37.48%)	0.78 (0.63, 0.96) 0.0167
Ticagrelor		
no	2705 (92.92%)	1.0
yes	206 (7.08%)	0.98 (0.64, 1.51) 0.9384
Dobutamine		
no	2771 (95.19%)	1.0
yes	140 (4.81%)	2.77 (2.12, 3.62) <0.0001
Dopamine		
no	2682 (92.13%)	1.0
yes	229 (7.87%)	2.38 (1.86, 3.05) <0.0001
Epinephrine		
no	2577 (88.53%)	1.0
yes	334 (11.47%)	1.68 (1.32, 2.13) <0.0001
Beta blockers		
no	1209 (41.53%)	1.0
yes	1702 (58.47%)	0.51 (0.42, 0.62) <0.0001
PTCA		
no	2883 (99.04%)	1.0
yes	28 (0.96%)	1.55 (0.64, 3.74) 0.3337
PCI		
no	2359 (81.04%)	1.0

yes	552 (18.96%)	0.78 (0.58, 1.05) 0.0988
CABG		
no	2391 (82.14%)	1.0
yes	520 (17.86%)	0.11 (0.05, 0.22) <0.0001
SAPSII	39.83 ± 14.06	1.05 (1.04, 1.05) <0.0001
SOFA	6.08 ± 3.99	1.18 (1.15, 1.20) <0.0001
ICU LOS (days)	4.30 ± 5.19	0.99 (0.98, 1.01) 0.3994

Exposure: GLR:Glucose-to-Lymphocyte Ratio;BUN: blood urea nitrogen; MBP:Mean Blood Pressure; SpO2: saturation of peripheral oxygen; WBC: white blood cell□RBC: red blood cell□SAPSII: simplified acute physiology score II; SOFA: sequential organ failure assessment score; MBP:mean blood pressure; PTCA:percutaneous transluminal coronary angioplasty;PCI:percutaneous coronary intervention; CABG: coronary artery bypass grafting; ICU LOS: Intensive care unit length of stay.

Table 3. Univariate and Multivariate Results by Cox Regression

Variable	Non-adjusted (HR,95% CI, *P*-value)	Adjusted I (HR,95%CI,*P*-value)	Adjusted II (HR,95%CI, *P*-value)
30-day mortality	1.02 (1.01, 1.02) <0.0001	1.02 (1.01, 1.02) <0.0001	1.01 (1.00, 1.02) 0.0134
GLR			
GLR (quartile)			
Q1(0.60-3.59)	1.0	1.0	1.0
Q2(3.60-6.06)	1.87 (1.30, 2.69) 0.0008	1.76 (1.22, 2.54) 0.0023	1.49 (1.02, 2.18) 0.0409
Q3(6.07-11.03)	2.20 (1.55, 3.12) <0.0001	2.07 (1.46, 2.95) <0.0001	1.56 (1.07, 2.26) 0.0203
Q4(11.04-97.55)	2.87 (2.05, 4.01) <0.0001	2.70 (1.93, 3.78) <0.0001	1.69 (1.17, 2.42) 0.0047
P for trend	1.35 (1.23, 1.48) <0.0001	1.33 (1.21, 1.46) <0.0001	1.14 (1.03, 1.26) 0.0107

Non-adjusted model.

Adjusted model I: adjusted for gender and age

Adjusted model II: adjusted for gender,age,hypertension,hyperlipidemia,atrial fibrillation,peripheral vasculard,cerebro vascular disea,rennal disease,malignant cancer,severe liver disease,heart rate,respiratory rate,temperature; SPO2,anion gap,BUN,bicarbonate,creatinine,monocytes,neutrophils,platelet,WBC,aspirin,

clopidogrel,dobutamine,dopamine,epinephrine,beta blockers.

Table 4 .Analysis of nonlinear relationship the GLR and 30-day Mortality

Inflection point of GLR	Hazard ratio (HR)	95% CI	*P*-value
≤4.66	1.33	1.07-1.65	0.0116
>4.66	1.01	1.00-1.02	0.2630

Adjusted variables: gender,age,hypertension,hyperlipidemia,atrial fibrillation,

peripheral vasculard,cerebro vascular disea,rennal disease,malignant cancer,severe liver disease,heart rate,respiratory rate,temperature; SPO2,anion gap,BUN,

bicarbonate,creatinine,monocytes,neutrophils,platelet,WBC,aspirin,clopidogrel,dobutamine,dopamine,epinephrine,beta blockers.

Figures

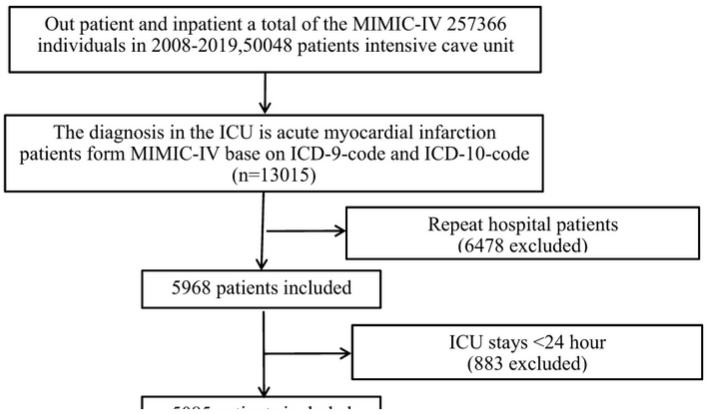

Figure 1

Flowchart of subject screening.

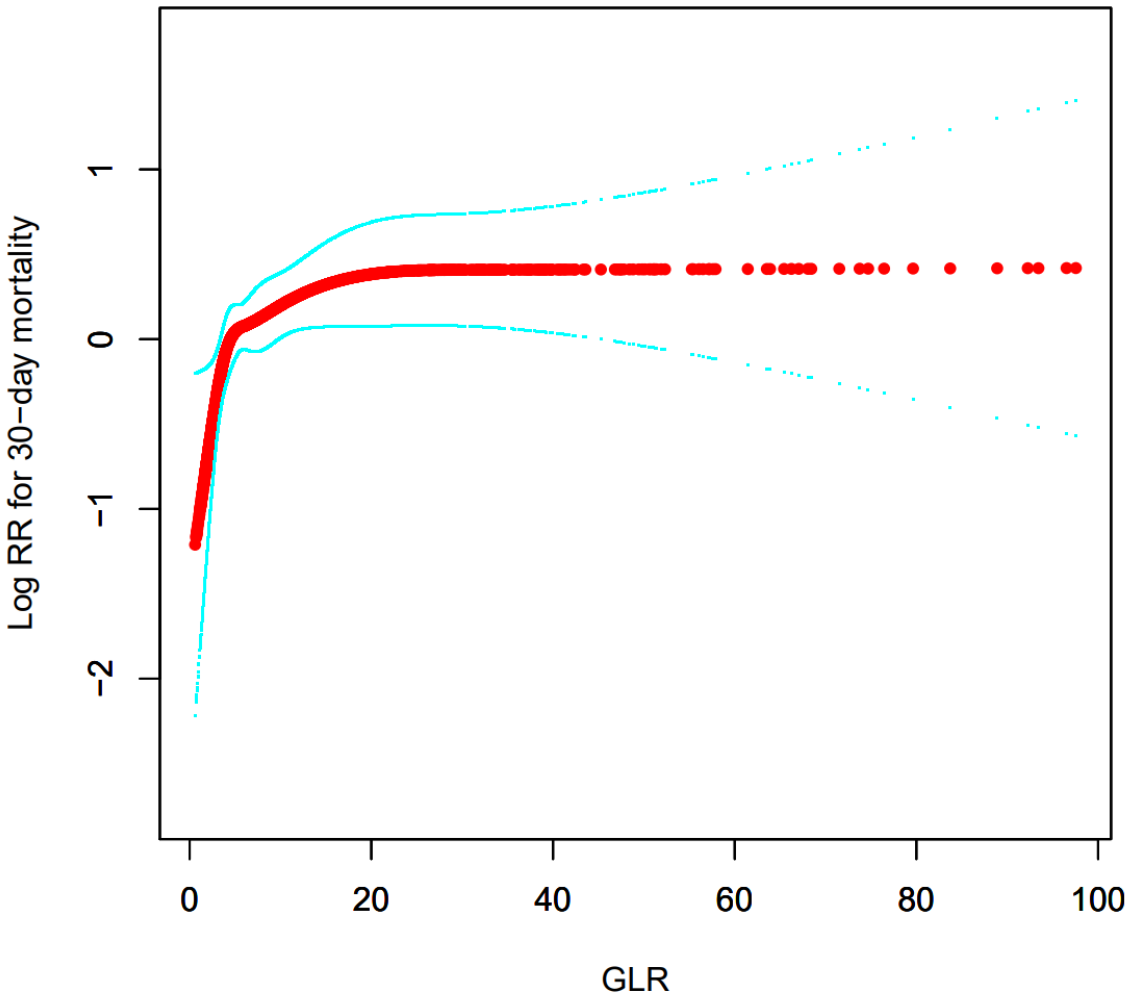

Figure 2

The nonlinear relationship between the GLR and 30-day Mortality