U-shaped Relationship Between Fibrinogen Level and the 10-year Mortality in Patients with Acute Coronary Syndrome: Prospective Cohort Study

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U-shaped Relationship Between Fibrinogen Level and the 10-year Mortality in Patients with Acute Coronary Syndrome: Prospective Cohort Study

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Abstract

Background: Identification of risk factors is essential in patients with coronary artery disease (CAD). As an important inflammatory factor and a key participant in coagulation, fibrinogen has attracted attention in the management of acute coronary syndrome (ACS). However, the relationship between the fibrinogen level and the prognosis of patients with ACS remains controversial.1 Our previous study found that fibrinogen was an independent risk factor for mortality during the follow-up in patients with CAD (adjusted HR: 1.40 (1.16–1.68)).2 In the ACS subgroup, no correlation was found between the fibrinogen level and mortality. In addition, the quantitative relationship between fibrinogen and the risk of mortality in a longer follow-up period needs further clarification.

Objective: To Identify the Relationship Between Fibrinogen Level and the 10-year Mortality in Patients with Acute Coronary Syndrome

Methods: We performed a prospective, large-scale, single-centre registry (ChiCTR2100049313) study to investigate the effect of fibrinogen on ACS prognoses. Patients were grouped by the five quantile levels of the plasma fibrinogen at admission. We used the Kaplan-Meier analysis to estimate the cumulative incidence of all-cause mortality. The predictive value of the fibrinogen level for the 10-year mortality was estimated by a Cox proportional hazards regression model. The impact of the fibrinogen on the 10-year mortality was assessed by a restricted cubic spline (RCS) curve, which was derived from an adjusted Cox proportional hazards regression model.

Results: The RCS curve suggested strong U-shaped relationships between the adjusted risk of the 10-year mortality and the fibrinogen level, which was in accordance with the trend found in the Kaplan-Meier analysis. The risk of all-cause mortality decreased until the fibrinogen reached 2.81 g/L, and it then started to increase afterwards (P for nonlinearity < 0.0001).

Conclusions: Kaplan-Meier curves (A) show a cumulative incidence of all-cause mortality at 10 years after it was stratified by five quantiles of the plasma fibrinogen level at admission. The restricted cubic-spline curve (B) shows the adjusted hazard ratio and its 95% confidence interval for the 10-year all-cause mortality based on the plasma fibrinogen level. The p-value for nonlinearity was < 0.001.

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Original Manuscript

U-shaped Relationship Between Fibrinogen Level and the 10-year Mortality in Patients with Acute Coronary Syndrome: Prospective Cohort Study

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Identification of risk factors is essential in patients with coronary artery disease (CAD). As an important inflammatory factor and a key participant in coagulation, fibrinogen has attracted attention in the management of acute coronary syndrome (ACS). Previous research has also demonstrated that as an acute-phase protein, the levels of fibrinogen and its degradation products are higher in COVID-19 patients than in healthy population[1]. However, the relationship between the fibrinogen level and the prognosis of patients with ACS remains controversial[2]. Our previous study found that fibrinogen was an independent risk factor for mortality during the follow-up in patients with CAD (adjusted HR: 1.40 (1.16–1.68))[3]. In the ACS subgroup, no correlation was found between the fibrinogen level and mortality. In addition, the quantitative relationship between fibrinogen and the risk of mortality in a longer follow-up period needs further clarification.

Method

We performed a prospective, large-scale, single-centre registry (ChiCTR2100049313) study to investigate the effect of fibrinogen on ACS prognoses. Patients were grouped by the five quantile levels of the plasma fibrinogen at admission. We used the Kaplan-Meier analysis to estimate the cumulative incidence of all-cause mortality. The predictive value of the fibrinogen level for the 10-year mortality was estimated by a Cox proportional hazards regression model. The impact of the fibrinogen on the 10-year mortality was assessed by a restricted cubic spline (RCS) curve, which was derived from an adjusted Cox proportional hazards regression model.

Ethical considerations: The study protocol was approved by the Institutional Review Board of West China Hospital in accordance with the Declaration of Helsinki (IRB number

2012□243□). All research data has been anonymized. Written informed consent was obtained before patients' enrollment. At the 10-year follow-up point, patients who come to the hospital for follow-up will be reimbursed for their transportation expenses.

Result

A total of 2434 consecutive ACS patients admitted to the West China Hospital between December 10th, 2010, and December 31st, 2012, were enrolled in this study. After exclusion of 29 patients with in-hospital mortality, 2405 patients were included in the analysis. The average age of the study population was 64.3 ± 11.1 years, and 78.3% of these patients were men. 36.0% of these ACS patients had STEMI, 16.7% had NSTEMI, and 47.3% had UA. The fibrinogen levels of these patients were normally distributed (skewness/kurtosis tests: $p < 0.001$), with an average level of 3.41 ± 1.06 g/L. The median follow-up time was 104 months (interquartile range: 98-111 months). In total, 387 patients (16.1%) died during the follow-up period. In the Kaplan-Meier analysis, the cumulative incidence of mortality was significantly different among the five groups (log-rank test: $p < 0.001$) (Figure 1A). Group 2 (fibrinogen level: 2.63-3.04 g/L) had the lowest incidence of mortality). In the Cox univariate regression analysis, fibrinogen was identified as an independent risk factor for the 10-year mortality (HR: 1.24 (1.15-1.35), $p < 0.001$). After adjusting for the cardiovascular risk factors, including age (per decade), sex, hypertension, diabetes, serum creatine level, LDL-C level, and Killip class, fibrinogen was still an independent risk factor (HR: HR 1.18 (1.08-1.29), $p<0.001$) for the 10-year mortality in the ACS patients. The fibrinogen category in the multivariate Cox model with the group 2 serving as referent showed the nonlinear trend to

mortality risk (Supplementary 1). Subgroup analysis suggests that in the STEMI/NSTEMI subgroup, the statistical results for fibrinogen show the same trend. However, this trend does not exist in the unstable angina subgroup (Supplementary 2).

We performed the RCS analysis in Stata software (version 16.1) with command *mkspline* and *xblc*. The knots were set as the quartile of fibrinogen level. The RCS curve suggested strong U-shaped relationships between the adjusted risk of the 10-year mortality and the fibrinogen level, which was in accordance with the trend found in the Kaplan-Meier analysis. The risk of all-cause mortality decreased until the fibrinogen reached 2.81 g/L, and it then started to increase afterwards (P for nonlinearity < 0.001).

Discussion

Acute-phase proteins are often associated with patient prognosis. For instance, higher levels of C-reactive protein typically indicate an increased in-hospital mortality among COVID-19 patients[4]. Previous epidemiologic suggested the elevated fibrinogen may mediate plaque rupture via prothrombotic or proinflammatory processes[2].However, a lower fibrinogen level may indicate a worse general physical condition and or may reveal hidden coagulation disorders in patients with ACS. Lower fibrinogen levels may be associated with reduced circulatory perfusion and internal environmental pH values. Previous research has demonstated that excessively low fibrinogen levels increase the in-hospital mortality of trauma patients[5]. In the present study, the long-term follow-up of nearly a decade (completion rate 94.78%) and the quantitative RCS analysis suggested that the fibrinogen levels at admission have a significant impact on the long-term prognosis of ACS patients. The mechanisms underlying this phenomenon may be that fibrinogen acts as both an acute-phase

protein and a subclinical inflammatory indicator. As an acute-phase protein, the fibrinogen level reflects the rupture of atherosclerotic plaques, while as a subclinical inflammatory indicator, it is involved in other metabolic processes, such as carbohydrate metabolism[6]. Both of these mechanisms may contribute to its impact on the patients' long-term prognoses.

The differences identified in the subgroup analysis may be due to variations in inflammatory levels and thrombotic markers between the populations with myocardial infarction and unstable angina[7]. The U-shape relationship between fibrinogen level and 10-year mortality suggested the need for long-term anti-inflammatory or metabolism treatment and the need to determine the fibrinogen level in patients with ACS. In addition, the nonlinear correlation between the fibrinogen and the long-term mortality may restrict the effect of fibrinogen in some risk models that were derived from extended linear regression. The predictive value of fibrinogen needs to be estimated in nonlinear functions or by using machine learning classifiers in further studies.

Disclosure: None of the authors declare any conflicts of interest in this paper.

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Data Availability：The anonymized dataset of this cohort can be requested by contacting the corresponding author via email.

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Figure legend

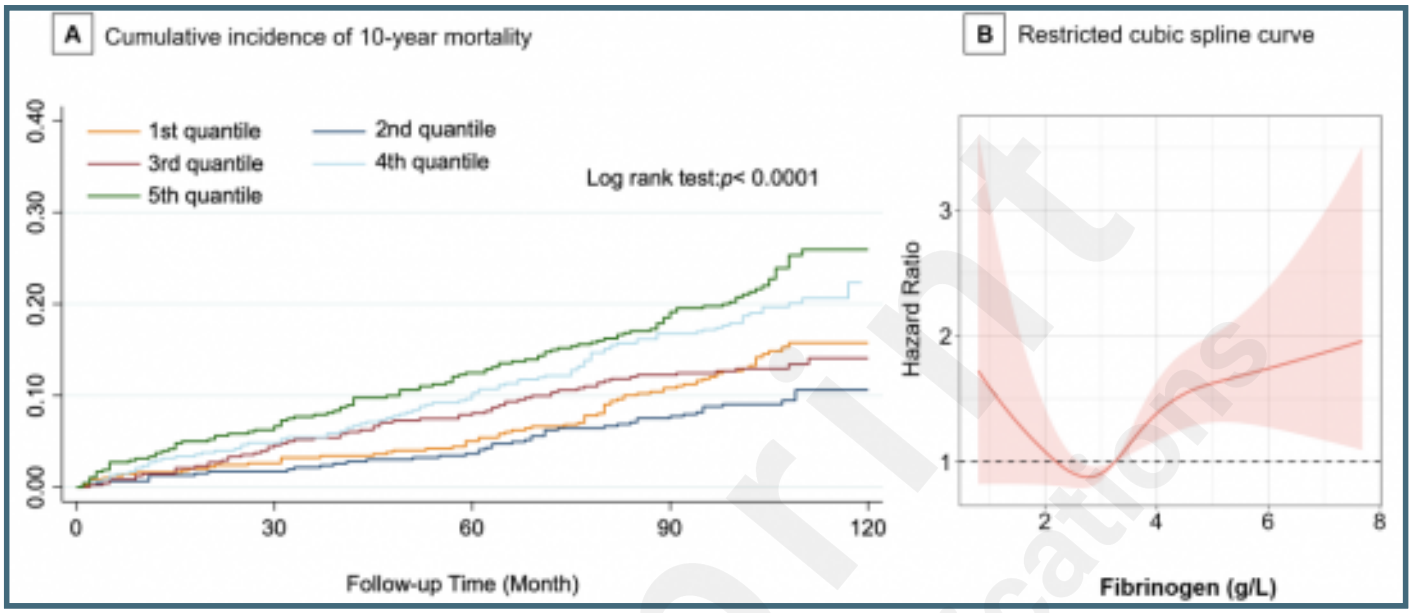
Figure 1: Cumulative Incidence of 10-Year All-Cause Mortality and Adjusted Hazard Ratio for 10-Year All-Cause Mortality.

Kaplan-Meier curves (A) show a cumulative incidence of all-cause mortality at 10 years after it was stratified by five quantiles of the plasma fibrinogen level at admission. The restricted cubic-spline curve (B) shows the adjusted hazard ratio and its 95% confidence interval for the 10-year all-cause mortality based on the plasma fibrinogen level. The p-value for nonlinearity was < 0.001.

Supplementary Files

Figures

Cumulative Incidence of 10-Year All-Cause Mortality and Adjusted Hazard Ratio for 10-Year All-Cause Mortality. Kaplan-Meier curves (A) show a cumulative incidence of all-cause mortality at 10 years after it was stratified by five quantiles of the plasma fibrinogen level at admission. The restricted cubic-spline curve (B) shows the adjusted hazard ratio and its 95% confidence interval for the 10-year all-cause mortality based on the plasma fibrinogen level. The p-value for nonlinearity was < 0.001.



Multimedia Appendixes

Multivariate Cox model and subgroup analysis.
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